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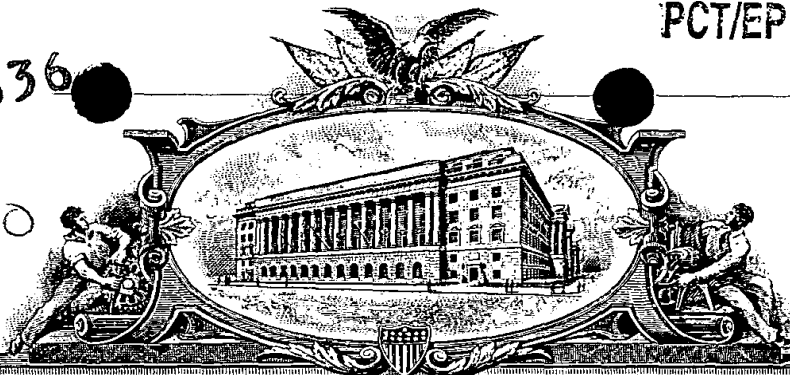
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APPLICATION NUMBER: 60/111,255

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET (Large Entity)

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

INVENTOR(S)/APPLICANT(S)					
Given Name (first and middle [if any])		Family Name or Surname		Residence (City and either State or Foreign Country)	
Zheng Xin		Dong		Framingham, Massachusetts	
<input type="checkbox"/> Additional inventors are being named on page 2 attached hereto					
TITLE OF THE INVENTION (280 characters max)					
ANALOGUES OF GLP-1					
CORRESPONDENCE ADDRESS					
Direct all correspondence to:					
<input type="checkbox"/> Customer Number <input type="text"/> → <div>Place Customer Number Bar Code Label here</div>					
OR					
<input checked="" type="checkbox"/> Firm or Individual Name		John D. Conway			
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ENCLOSED APPLICATION PARTS (check all that apply)					
<input checked="" type="checkbox"/> Specification		Number of Pages		33	
<input type="checkbox"/> Drawing(s)		Number of Sheets		<input checked="" type="checkbox"/> Other (specify)	
				Claims: 6 pgs; Abstract: 1 pg.	
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)					
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government					
<input checked="" type="checkbox"/> No.					
<input type="checkbox"/> Yes, the name of the U.S. Government agency and the Government contract number are.					

Respectfully submitted,

SIGNATURE



DATE

December 7, 1998

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6011255-120798

Patent
Attorney Docket No.: BPC089P

**PROVISIONAL APPLICATION
UNDER 37 CFR 1.53(b)(2)**

TITLE: ANALOGUES OF GLP-1

APPLICANT: ZHENG XIN DONG

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ANALOGUES OF GLP-1

Background of the Invention

The present invention is directed to peptide analogues of glucagon-like peptide-1, the pharmaceutically-acceptable salts thereof, to methods of using such analogues to treat mammals and to pharmaceutical compositions useful therefor comprising said analogues.

Glucagon-like peptide-1 (7-36) amide (GLP-1) is synthesized in the intestinal L-cells by tissue-specific post-translational processing of the glucagon precursor preproglucagon (Varndell, J.M., et al., J. Histochem Cytochem, 1985:33:1080-6) and is released into the circulation in response to a meal. The plasma concentration of GLP-1 rises from a fasting level of approximately 15 pmol/L to a peak postprandial level of 40 pmol/L. It has been demonstrated that, for a given rise in plasma glucose concentration, the increase in plasma insulin is approximately threefold greater when glucose is administered orally compared with intravenously (Kreymann, B., et al., Lancet 1987:2, 1300-4). This alimentary enhancement of insulin release, known as the incretin effect, is primarily humoral and GLP-1 is now thought to be the most potent physiological incretin in humans. In addition to the insulinotropic effect, GLP-1 suppresses glucagon secretion, delays gastric emptying (Wettergren A., et al., Dig Dis Sci 1993:38:665-73) and may enhance peripheral glucose disposal (D'Alessio, D.A. et al., J. Clin Invest 1994:93:2293-6).

In 1994, the therapeutic potential of GLP-1 was suggested following the observation that a single subcutaneous (s/c) dose of GLP-1 could completely normalize postprandial glucose levels in patients with non-insulin-dependent diabetes mellitus (NIDDM) (Gutniak, M.K., et al., Diabetes Care 1994:17:1039-44). This effect was thought to be mediated both by increased insulin release and by a reduction in glucagon secretion. Furthermore, an intravenous infusion of GLP-1 has been shown to delay postprandial gastric emptying in patients with NIDDM (Williams, B., et al., J. Clin Endo Metab 1996:81:327-32). Unlike sulphonylureas, the insulinotropic action of GLP-1 is dependent on plasma glucose concentration (Holz, G.G. 4th, et al., Nature 1993:361:362-5). Thus, the loss of GLP-1-mediated insulin release at low plasma glucose concentration protects against severe hypoglycemia. This combination of actions gives GLP-1 unique potential therapeutic advantages over other agents currently used to treat NIDDM.

Numerous studies have shown that when given to healthy subjects, GLP-1 potently influences glycemic levels as well as insulin and glucagon concentrations (Orskov, C,

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Diabetologia 35:701-711, 1992; Holst, J.J., et al., Potential of GLP-1 in diabetes management in Glucagon III, Handbook of Experimental Pharmacology, Lefebvre PJ, Ed. Berlin, Springer Verlag, 1996, p. 311-326), effects which are glucose dependent (Kreymann, B., et al., Lancet ii: 1300-1304, 1987; Weir, G.C., et al., Diabetes 38:338-342, 1989). Moreover, it is also effective in patients with diabetes (Gutniak, M., N. Engl J Med 226:1316-1322, 1992; Nathan, D.M., et al., Diabetes Care 15:270-276, 1992), normalizing blood glucose levels in type 2 diabetic subjects (Nauck, M.A., et al., Diabetologia 36:741-744, 1993), and improving glycemic control in type 1 patients (Creutzfeldt, W.O., et al., Diabetes Care 19:580-586, 1996), raising the possibility of its use as a therapeutic agent.

10 GLP-1 is, however, metabolically unstable, having a plasma half-life ($t_{1/2}$) of only 1-2 min *in vivo*. Exogenously administered GLP-1 is also rapidly degraded (Deacon, C.F., et al., Diabetes 44:1126-1131, 1995). This metabolic instability limits the therapeutic potential of native GLP-1. Hence, there is a need for GLP-1 analogues that are more active or are more metabolically stable than native GLP-1.

15 Summary of the Invention

In one aspect, the present invention is directed to a compound of formula (I),
 $(R^2R^3)-A^7-A^8-A^9-A^{10}-A^{11}-A^{12}-A^{13}-A^{14}-A^{15}-A^{16}-A^{17}-A^{18}-A^{19}-A^{20}-A^{21}-A^{22}-A^{23}-A^{24}-A^{25}-A^{26}-A^{27}-A^{28}-A^{29}-A^{30}-A^{31}-A^{32}-A^{33}-A^{34}-A^{35}-A^{36}-A^{37}-A^{38}-R^1,$

(I)

20 wherein

A^7 is L-His, Ura, Paa, Pta, Amp, Tma-His, or deleted, provided that when A^7 is Ura, Paa or Pta, then R^2 and R^3 are deleted;

A^8 is Ala, D-Ala, Aib, Acc, N-Me-Ala, N-Me-D-Ala or N-Me-Gly;

A^9 is Glu, N-Me-Glu, N-Me-Asp or Asp;

25 A^{10} is Gly, Acc or Aib;

A^{11} is Thr or Ser;

A^{12} is Phe, Acc, Aic, Aib, 3-Pal, 4-Pal, β -Nal, Cha, Trp or X^1 -Phe;

A^{13} is Thr or Ser;

A^{14} is Ser or Aib;

30 A^{15} is Asp or Glu;

A^{16} is Val, Acc, Aib, Leu, Ile, Tle, Nle, Abu, Ala or Cha;

A^{17} is Ser or Thr;

A^{18} is Ser or Thr;

A^{19} is Tyr, Cha, Phe, 3-Pal, 4-Pal, Acc, β -Nal or X^1 -Phe;

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A²⁰ is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Val, Phe or X¹-Phe;

A²¹ is Glu or Asp;

A²² is Gly, Acc, β-Ala or Aib;

A²³ is Gln, Asp, Asn or Glu;

5 A²⁴ is Ala, Aib, Val, Abu, Tle or Acc;

A²⁵ is Ala, Aib, Val, Abu, Tle, Acc, Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)_e-X³)-C(O);

A²⁶ is Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)_e-X³)-C(O);

A²⁷ is Glu or Asp;

10 A²⁸ is Phe, Pal, β-Nal, X¹-Phe, Aic, Acc, Aib, Cha or Trp;

A²⁹ is Ile, Acc, Aib, Leu, Nle, Cha, Tle, Val, Abu, Ala or Phe;

A³⁰ is Ala, Aib or Acc;

A³¹ is Trp, β-Nal, 3-Pal, 4-Pal, Phe, Acc, Aib or Cha;

A³² is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Phe, X¹-Phe or Ala;

15 A³³ is Val, Acc, Aib, Leu, Ile, Tle, Nle, Cha, Ala, Phe, Abu or X¹-Phe;

A³⁴ is Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)_e-X³)-C(O);

A³⁵ is Gly, β-Ala, D-Ala, Gaba, Ava, HN-(CH₂)_m-C(O), Aib, Acc or a D-amino acid;

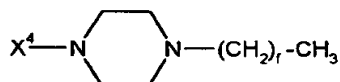
A³⁶ is L- or D-Arg, D- or L-Lys, D- or L-hArg, D- or L-Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O), HN-CH((CH₂)_e-X³)-C(O) or deleted;

20 A³⁷ is Gly, β-Ala, D-Ala, Gaba, Ava, HN-(CH₂)_m-C(O), Aib, Acc, Ado, a D-amino acid or deleted;

A³⁸ is D- or L-Lys, D- or L-Arg, D- or L-hArg, D- or L-Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O), HN-CH((CH₂)_e-X³)-C(O) or deleted;

25 X¹ for each occurrence is independently selected from the group consisting of (C₁-C₆)alkyl, OH and halo;

R¹ is OH, NH₂, (C₁-C₃₀)alkoxy, or NH-X²-CH₂-Z, wherein X² is a (C₁-C₃₀)hydrocarbon moiety, and Z is H, OH, CO₂H or CONH₂;

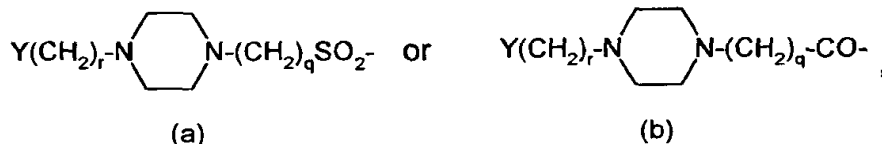


X³ is or -C(O)-NHR¹², wherein X⁴ for each occurrence is independently -C(O)-, -NH-C(O)- or -CH₂-, and f for each occurrence is independently an integer from 1 to 29;

30 each of R² and R³ is, independently selected from the group consisting of H, (C₁-C₃₀)alkyl, (C₂-C₃₀)alkenyl, phenyl(C₁-C₃₀)alkyl, naphthyl(C₁-C₃₀)alkyl, hydroxy(C₁-

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C₃₀)alkyl, hydroxy(C₂-C₃₀)alkenyl, hydroxyphenyl(C₁-C₃₀)alkyl, and hydroxynaphthyl(C₁-C₃₀)alkyl; or one of R² and R³ is $(\text{CH}_3)_2\text{-N}^+\text{-C}=\text{N}^+(\text{CH}_3)_2$, (C₁-C₃₀)acyl, (C₁-C₃₀)alkylsulfonyl, C(O)X⁵,



5 where Y is H, OH or NH₂; r is 0 to 4; q is 0 to 4; X⁵ is (C₁-C₃₀)alkyl, (C₂-C₃₀)alkenyl, phenyl(C₁-C₃₀)alkyl, naphthyl(C₁-C₃₀)alkyl, hydroxy(C₁-C₃₀)alkyl, hydroxy(C₂-C₃₀)alkenyl, hydroxyphenyl(C₁-C₃₀)alkyl or hydroxynaphthyl(C₁-C₃₀)alkyl;

10 e for each occurrence is independently an integer from 1 to 4;
m for each occurrence is independently an integer from 5-24;
n for each occurrence is independently an integer from 1-5;
R¹⁰ and R¹¹ for each occurrence is each independently H, (C₁-C₃₀)alkyl, (C₁-C₃₀)acyl, (C₁-C₃₀)alkylsulfonyl, -C((NH)(NH₂)) or



15 C₃₀)alkylsulfonyl, -C((NH)(NH₂)) or (C₁-C₃₀)alkyl; and
R¹² is (C₁-C₃₀)alkyl;

with the proviso that:

- 20 (i) at least one amino acid of a compound of formula (I) is not the same as the native sequence of hGLP-1(7-36, -37 or -38)NH₂ or hGLP-1(7-36, -37 or -38)OH;
(ii) a compound of formula (I) is not an analogue of hGLP-1(7-36, -37 or -38)NH₂ or hGLP-1(7-36, -37 or -38)OH wherein a single position has been substituted by Ala;
(iii) a compound of formula (I) is not [Arg^{26,34}, Lys³⁸]hGLP-1(7-38)-E, [Lys²⁶(N^ε-alkanoyl)]hGLP-1(7-36, -37 or -38)-E, [Lys³⁴(N^ε-alkanoyl)]hGLP-1(7-36, -37 or -38)-E,
25 [Lys^{26,34}-bis(N^ε-alkanoyl)]hGLP-1(7-36, -37 or -38)-E, [Arg²⁶, Lys³⁴(N^ε-alkanoyl)]hGLP-1(8-

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36, -37 or -38)-E, [Arg^{26,34}, Lys³⁶(N^f-alkanoyl)]hGLP-1(7-36, -37 or -38)-E or [Arg^{26,34}, Lys³⁸(N^f-alkanoyl)]hGLP-1(7-38)-E, wherein E is -OH or -NH₂;

(iv) a compound of formula (I) is not Z-hGLP-1(7-36, -37 or -38)-OH, Z-hGLP-1(7-36, -37 or -38)-NH₂, where Z is selected from the group consisting of

5 (a) [Arg²⁶], [Arg³⁴], [Arg^{26,34}], [Lys³⁶], [Arg²⁶, Lys³⁶], [Arg³⁴, Lys³⁶], [D-Lys³⁶], [Arg³⁶], [D-Arg³⁶], [Arg^{26,34}, Lys³⁶] or [Arg^{26,36}, Lys³⁴];

(b) [Asp²¹];

(c) at least one of [Aib⁸], [D-Ala⁸] and [Asp⁹]; and

(d) [Tyr⁷], [N-acyl-His⁷], [N-alkyl-His⁷], [N-acyl-D-His⁷] or [N-alkyl-D-His⁷];

10 (v) a compound of formula (I) is not a combination of any two of the substitutions listed in groups (a) to (d); and

(vi) a compound of formula (I) is not [N-Me-Ala⁸]hGLP-1(8-36 or -37), [Glu¹⁵]hGLP-1(7-36 or -37), [Asp²¹]hGLP-1(7-36 or -37) or [Phe³¹]hGLP-1(7-36 or -37).

A preferred group of compounds of the immediately foregoing compound, is where

15 A¹¹ is Thr; A¹³ is Thr; A¹⁵ is Asp; A¹⁷ is Ser; A¹⁸ is Ser; A²¹ is Glu; A²³ is Gln or Glu; A²⁷ is Glu; and A³¹ is Trp; or a pharmaceutically acceptable salt thereof.

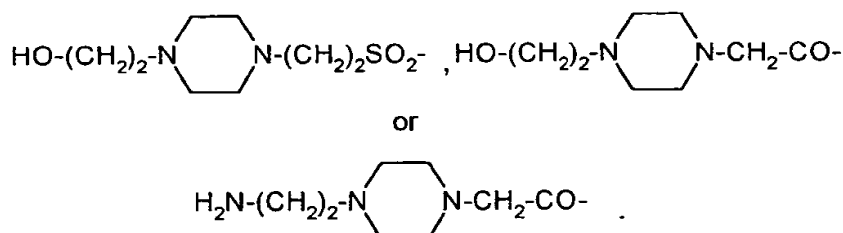
A preferred group of compounds of the immediately foregoing group of compounds is where A⁹ is Glu, N-Me-Glu or N-Me-Asp; A¹² is Phe, Acc or Aic; A¹⁶ is Val, Acc or Aib; A¹⁹ is Tyr; A²⁰ is Leu, Acc or Cha; A²⁴ is Ala, Aib or Acc; A²⁵ is Ala, Aib, Acc, Lys, Arg, hArg, 20 Om, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)_e-X³)-C(O); A²⁸ is Phe; A²⁹ is Ile or Acc; A³⁰ is Ala or Aib; A³² is Leu, Acc or Cha; and A³³ is Val or Acc; or a pharmaceutically acceptable salt thereof.

A preferred group of compounds of the immediately foregoing group of compounds is where A⁸ is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A¹⁰ is Gly; A¹² 25 is Phe, A6c or A5c; A¹⁶ is Val, A6c or A5c; A²⁰ is Leu, A6c, A5c or Cha; A²² is Gly, β-Ala or Aib; A²⁴ is Ala or Aib; A²⁹ is Ile, A6c or A5c; A³² is Leu, A6c, A5c or Cha; A³³ is Val, A6c or A5c; A³⁵ is Aib, β-Ala, Ado, A6c, A5c or Gly; and A³⁷ is Gly, Aib, β-Ala, Ado, D-Ala or deleted; or a pharmaceutically acceptable salt thereof.

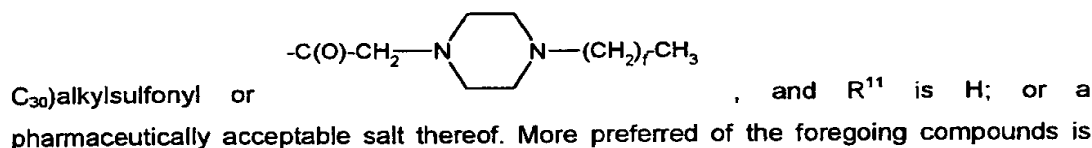
A preferred group of compounds of the immediately foregoing group of compounds 30 is where X⁴ for each occurrence is -C(O)-; e for each occurrence is independently 1 or 2; and R¹ is OH or NH₂, or a pharmaceutically acceptable salt thereof.

A preferred group of compounds of the immediately foregoing group of compounds or a pharmaceutically acceptable salt thereof is where R² is H and R³ is (C₁-C₃₀)alkyl, (C₂-C₃₀)alkenyl, (C₁-C₃₀)acyl, (C₁-C₃₀)alkylsulfonyl,

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- A preferred compound of the formula (I) is where A⁸ is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A¹⁰ is Gly; A¹² is Phe, A6c or A5c; A¹⁸ is Val, A6c or A5c; A²⁰ is Leu, A6c, A5c or Cha; A²² is Gly, β-Ala or Aib; A²⁴ is Ala or Aib; A²⁹ is Ile, A6c or A5c; A³² is Leu, A6c, A5c or Cha; A³³ is Val, A6c or A5c; A³⁵ is Aib, β-Ala, Ado, A6c, A5c or Gly; and A³⁷ is Gly, Aib, β-Ala, Ado, D-Ala or deleted; X⁴ for each occurrence is -C(O)-; e for each occurrence is independently 1 or 2; R¹ is OH or NH₂; R¹⁰ is (C₁-C₃₀)acyl, (C₁-



- $$-\text{C}(\text{O})-\text{CH}_2-\text{N} \begin{array}{c} \diagup \diagdown \\ \diagdown \diagup \end{array} \text{N}-(\text{CH}_2)_f\text{CH}_3$$
- 10 where R¹⁰ is (C₄-C₂₀)acyl, (C₄-C₂₀)alkylsulfonyl or , or a pharmaceutically acceptable salt thereof.

- A more preferred compound of formula (I) is where said compound is of the formula
- [Aib^{8,35}]hGLP-1(7-36)NH₂,
- [(N^α-HEPES-His)⁷, Aib^{8,35}]hGLP-1(7-36)NH₂,
- 15 [(N^α-HEPA-His)⁷, Aib^{8,35}]hGLP-1(7-36)NH₂,
- [Aib⁸, β-Ala³⁵]hGLP-1(7-36)NH₂,
- [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂,
- [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂,
- [Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)NH₂,
- 20 [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-decanoyl)]hGLP-1(7-36)NH₂,
- [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-dodecanesulfonyl)]hGLP-1(7-36)NH₂,
- [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂,
- [Aib^{8,35}, Arg^{26,34}, Asp³⁶(1-(4-tetradecyl-piperazine))]hGLP-1(7-36)NH₂,
- [Aib^{8,35}, Arg^{26,34}, Asp³⁶(1-tetradecylamino)]hGLP-1(7-36)NH₂,

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[Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl), β-Ala³⁷]hGLP-1(7-37)-OH or
[Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)-OH, or a pharmaceutically
acceptable salt thereof.

- More preferred of the immediately foregoing group of compounds is a compound of
- 5 the formula
- [Aib^{8,35}]hGLP-1(7-36)NH₂,
[Aib⁸, β-Ala³⁵]hGLP-1(7-36)NH₂,
[Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂,
[Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)NH₂,
10 [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-decanoyl)]hGLP-1(7-36)NH₂, or
[Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl), β-Ala³⁷]hGLP-1(7-37)-OH, or a pharmaceutically
acceptable salt thereof.

- Another more preferred compound of formula (I) is each of the compounds that are
specifically enumerated hereinbelow in the Examples section of the present disclosure, or a
15 pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides a pharmaceutical composition
comprising an effective amount of a compound of formula (I) as defined hereinabove or a
pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or
diluent.

- 20 In yet another aspect, the present invention provides a method of eliciting an agonist
effect from a GLP-1 receptor in a subject in need thereof which comprises administering to
said subject an effective amount of a compound of formula (I) as defined hereinabove or a
pharmaceutically acceptable salt thereof.

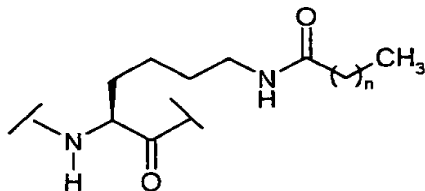
- In a further aspect, the present invention provides a method of treating a disease
25 selected from the group consisting of Type I diabetes, Type II diabetes, obesity,
glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis,
central nervous system disease, restenosis and neurodegenerative disease, in a subject in
need thereof which comprises administering to said subject an effective amount of a
compound of formula (I) as defined hereinabove or a pharmaceutically acceptable salt
30 thereof. A preferred method of the immediately foregoing method is where the disease
being treated is Type I diabetes or Type II diabetes.

With the exception of the N-terminal amino acid, all abbreviations (e.g. Ala) of amino
acids in this disclosure stand for the structure of -NH-CH(R)-CO-, wherein R is the side

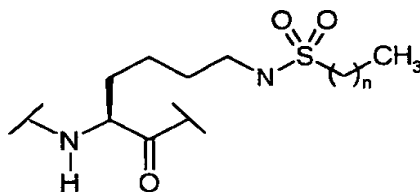
chain of an amino acid (e.g., CH₃ for Ala). For the N-terminal amino acid, the abbreviation stands for the structure of (R²R³)-N-CH(R)-CO-, wherein R is a side chain of an amino acid and R² and R³ are as defined above, except when A⁷ is Ura, Paa or Pta, in which case R² and R³ are not present since Ura, Paa and Pta are considered here as des-amino amino acids. Amp, β-Nal, Nle, Cha, 3-Pal, 4-Pal and Aib are the abbreviations of the following α-amino acids: 4-amino-phenylalanine, β-(2-naphthyl)alanine, norleucine, cyclohexylalanine, β-(3-pyridinyl)alanine, β-(4-pyridinyl)alanine and α-aminoisobutyric acid, respectively. Other amino acid definitions are: Ura is urocanic acid; Pta is (4-pyridylthio) acetic acid; Paa is *trans*-3-(3-pyridyl) acrylic acid; Tma-His is N,N-tetramethylamidino-histidine; N-Me-Ala is N-methyl-alanine; N-Me-Gly is N-methyl-glycine; N-Me-Glu is N-methyl-glutamic acid; Tle is *tert*-butylglycine; Abu is α-aminobutyric acid; Tba is *tert*-butylalanine; Orn is ornithine; Aib is α-aminoisobutyric acid; β-Ala is β-alanine; Gaba is γ-aminobutyric acid; Ava is 5-aminovaleric acid; Ado is 12-aminododecanoic acid and Aic is 2-aminoindane-2-carboxylic acid.

What is meant by Acc is an amino acid selected from the group of 1-amino-1-cyclopropanecarboxylic acid (A3c); 1-amino-1-cyclobutanecarboxylic acid (A4c); 1-amino-1-cyclopentanecarboxylic acid (A5c); 1-amino-1-cyclohexanecarboxylic acid (A6c); 1-amino-1-cycloheptanecarboxylic acid (A7c); 1-amino-1-cyclooctanecarboxylic acid (A8c); and 1-amino-1-cyclononanecarboxylic acid (A9c). In the above formula, hydroxyalkyl, hydroxyphenylalkyl, and hydroxynaphthylalkyl may contain 1-4 hydroxy substituents. COX⁵ stands for -C=O-X⁵. Examples of -C=O-X⁵ include, but are not limited to, acetyl and phenylpropionyl.

What is meant by Lys(N^E-alkanoyl) is represented by the following structure:



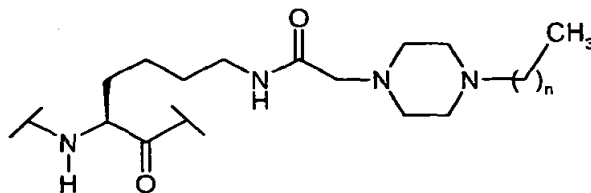
. What is meant by Lys(N^E-alkylsulfonyl) is represented



by the following structure:

. What is meant by Lys(N^E-

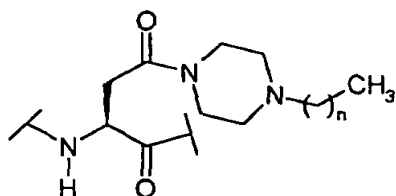
(2-(4-alkyl-1-piperazine)-acetyl)) is represented by the following



structure:

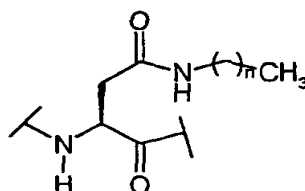
. What is meant by Asp(1-(4-

alkyl-piperazine)) is represented by the following



structure:

. What is meant by Asp(1-alkylamino) is



5 represented by the following structure:
The foregoing structures is 1-30.

. The variable n in the

The full names for other abbreviations used herein are as follows: Boc for t-butylloxycarbonyl, HF for hydrogen fluoride, Fm for formyl, Xan for xanthyl, Bzl for benzyl, Tos for tosyl, DNP for 2,4-dinitrophenyl, DMF for dimethylformamide, DCM for dichloromethane, HBTU for 2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate, DIEA for diisopropylethylamine, HOAc for acetic acid, TFA for trifluoroacetic acid, 2ClZ for 2-chlorobenzyloxycarbonyl, 2BrZ for 2-bromobenzyloxycarbonyl, OcHex for O-cyclohexyl, Fmoc for 9-fluorenylmethoxycarbonyl, HOBt for N-hydroxybenzotriazole and PAM resin for 4-
10
15 hydroxymethylphenylacetamidomethyl resin.

The term "halo" encompasses fluoro, chloro, bromo and iodo.

The term "(C₁-C₁₂)hydrocarbon moiety" encompasses alkyl, alkenyl and alkynyl and in the case of alkenyl and alkynyl there are C₂-C₁₂.

A peptide of this invention is also denoted herein by another format, e.g.,
20 [A5c⁸]hGLP-1(7-36)NH₂, with the substituted amino acids from the natural sequence placed between the set of brackets (e.g., A5c⁸ for Ala⁸ in hGLP-1). The abbreviation GLP-1 means

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glucagon-like peptide-1. The numbers between the parentheses refer to the number of amino acids present in the peptide (e.g., hGLP-1(7-36) is amino acids 7 through 36 of the peptide sequence for human GLP-1). The sequence for hGLP-1(7-37) is listed in Mojsov, S., Int. J. Peptide Protein Res., 40, 1992, pp. 333-342. The designation "NH₂" in hGLP-1(7-36)NH₂ indicates that the C-terminus of the peptide is amidated. hGLP-1(7-36) means that the C-terminus is the free acid. In hGLP-1(7-38), residues in positions 37 and 38 are Gly and Arg, respectively.

Detailed Description

The peptides of this invention can be prepared by standard solid phase peptide synthesis. See, e.g., Stewart, J.M., et al., Solid Phase Synthesis (Pierce Chemical Co., 2d ed. 1984). The substituents R² and R³ of the above generic formula may be attached to the free amine of the N-terminal amino acid by standard methods known in the art. For example, alkyl groups, e.g., (C₁-C₃₀)alkyl, may be attached using reductive alkylation. Hydroxyalkyl groups, e.g., (C₁-C₃₀)hydroxyalkyl, may also be attached using reductive alkylation wherein the free hydroxy group is protected with a t-butyl ester. Acyl groups, e.g., COE¹, may be attached by coupling the free acid, e.g., E¹COOH, to the free amine of the N-terminal amino acid by mixing the completed resin with 3 molar equivalents of both the free acid and diisopropylcarbodiimide in methylene chloride for one hour. If the free acid contains a free hydroxy group, e.g., p-hydroxyphenylpropionic acid, then the coupling should be performed with an additional 3 molar equivalents of HOBt.

When R¹ is NH-X²-CH₂-Z (Z=CONH₂), the synthesis of the peptide starts with BocHN-X²-CH₂-COOH which is coupled to the MBHA resin. If R¹ is NH-X²-CH₂-COOH (Z=COOH) the synthesis of the peptide starts with Boc-HN-X²-CH₂-COOH which is coupled to PAM resin. For this particular step, 4 molar equivalents of Boc-HN-X²-COOH, HBTU and HOBt and 10 molar equivalents of DIEA are used. The coupling time is about 8 hours.

The protected amino acid 1-[N-tert-butoxycarbonyl-amino]-1-cyclohexane-carboxylic acid (Boc-A6c-OH) was synthesized as follows. 19.1 g (0.133 mol) of 1-amino-1-cyclohexanecarboxylic acid (Acros Organics, Fisher Scientific, Pittsburgh, PA) was dissolved in 200 ml of dioxane and 100 ml of water. To it was added 67 ml of 2N NaOH. The solution was cooled in an ice-water bath. 32.0 g (0.147 mol) of di-tert-butyl-dicarbonate was added to this solution. The reaction mixture was stirred overnight at room temperature. Dioxane was then removed under reduced pressure. 200 ml of ethyl acetate was added to the remaining aqueous solution. The mixture was cooled in an ice-water bath. The pH of the aqueous layer was adjusted to about 3 by adding 4N HCl. The organic

layer was separated. The aqueous layer was extracted with ethyl acetate (1 x 100 ml). The two organic layers were combined and washed with water (2 x 150 ml), dried over anhydrous MgSO_4 , filtered, and concentrated to dryness under reduced pressure. The residue was recrystallized in ethyl acetate/hexanes. 9.2 g of the pure product was obtained. 29% yield.

Boc-A5c-OH was synthesized in an analogous manner to that of Boc-A6c-OH. Other protected Acc amino acids can be prepared in an analogous manner by a person of ordinary skill in the art as enabled by the teachings herein.

In the synthesis of a GLP-1 analogue of this invention containing A5c, A6c and/or Aib, the coupling time is 2 hrs. for these residues and the residue immediately following them. For the synthesis of $[\text{Tma-His}^7]\text{hGLP-1(7-36)NH}_2$, HBTU (2 mmol) and DIEA (1.0 ml) in 4 ml DMF are used to react with the N-terminal free amine of the peptide-resin in the last coupling reaction; the coupling time is about 2 hours.

The substituents R^2 and R^3 of the above generic formula can be attached to the free amine of the N-terminal amino acid by standard methods known in the art. For example, alkyl groups, e.g., $(\text{C}_1\text{-C}_{30})\text{alkyl}$, can be attached using reductive alkylation. Hydroxyalkyl groups, e.g., $(\text{C}_1\text{-C}_{30})\text{hydroxyalkyl}$, can also be attached using reductive alkylation wherein the free hydroxy group is protected with a t-butyl ester. Acyl groups, e.g., COX^1 , can be attached by coupling the free acid, e.g., X^1COOH , to the free amine of the N-terminal amino acid by mixing the completed resin with 3 molar equivalents of both the free acid and diisopropylcarbodiimide in methylene chloride for about one hour. If the free acid contains a free hydroxy group, e.g., p-hydroxyphenylpropionic acid, then the coupling should be performed with an additional 3 molar equivalents of HOBt.

A compound of the present invention can be tested for activity as a GLP-1 binding compound according to the following procedure.

Cell Culture:

RIN 5F rat insulinoma cells (ATCC-# CRL-2058, American Type Culture Collection, Manassas, VA), expressing the GLP-1 receptor, were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal calf serum, and maintained at about 37 °C in a humidified atmosphere of 5% CO_2 /95% air.

Radioligand Binding:

Membranes were prepared for radioligand binding studies by homogenization of the RIN cells in 20 ml of ice-cold 50 mM Tris-HCl with a Brinkman Polytron (Westbury, NY) (setting 6, 15 sec). The homogenates were washed twice by centrifugation (39,000 g / 10

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min), and the final pellets were resuspended in 50 mM Tris-HCl, containing 2.5 mM MgCl₂, 0.1 mg/ml bacitracin (Sigma Chemical, St. Louis, MO), and 0.1% BSA. For assay, aliquots (0.4 ml) were incubated with 0.05 nM [¹²⁵I]GLP-1(7-36) (~2200 Ci/mmol, New England Nuclear, Boston, MA), with and without 0.05 ml of unlabeled competing test peptides. After a 100 min incubation (25 °C), the bound [¹²⁵I]GLP-1(7-36) was separated from the free by rapid filtration through GF/C filters (Brandel, Gaithersburg, MD), which had been previously soaked in 0.5% polyethyleneimine. The filters were then washed three times with 5 ml aliquots of ice-cold 50 mM Tris-HCl, and the bound radioactivity trapped on the filters was counted by gamma spectrometry (Wallac LKB, Gaithersburg, MD). Specific binding was defined as the total [¹²⁵I]GLP-1(7-36) bound minus that bound in the presence of 1000 nM GLP1(7-36) (Bachem, Torrence, CA).

The peptides of this invention can be provided in the form of pharmaceutically acceptable salts. Examples of such salts include, but are not limited to, those formed with organic acids (e.g., acetic, lactic, maleic, citric, malic, ascorbic, succinic, benzoic, methanesulfonic, toluenesulfonic, or pamoic acid), inorganic acids (e.g., hydrochloric acid, sulfuric acid, or phosphoric acid), and polymeric acids (e.g., tannic acid, carboxymethyl cellulose, polylactic, polyglycolic, or copolymers of polylactic-glycolic acids). A typical method of making a salt of a peptide of the present invention is well known in the art and can be accomplished by standard methods of salt exchange. Accordingly, the TFA salt of a peptide of the present invention (the TFA salt results from the purification of the peptide by using preparative HPLC, eluting with TFA containing buffer solutions) can be converted into another salt, such as an acetate salt by dissolving the peptide in a small amount of 0.25 N acetic acid aqueous solution. The resulting solution is applied to a semi-prep HPLC column (Zorbax, 300 SB, C-8). The column is eluted with (1) 0.1N ammonium acetate aqueous solution for 0.5 hrs., (2) 0.25N acetic acid aqueous solution for 0.5 hrs. and (3) a linear gradient (20% to 100% of solution B over 30 min.) at a flow rate of 4 ml/min (solution A is 0.25N acetic acid aqueous solution; solution B is 0.25N acetic acid in acetonitrile/water, 80:20). The fractions containing the peptide are collected and lyophilized to dryness.

As is well known to those skilled in the art, the known and potential uses of GLP-1 is varied and multitudinous [See, Todd, J.F., et al., Clinical Science, 1998, 95, pp. 325-329; and Todd, J.F. et al., European Journal of Clinical Investigation, 1997, 27, pp.533-536]. Thus, the administration of the compounds of this invention for purposes of eliciting an agonist effect can have the same effects and uses as GLP-1 itself. These varied uses of GLP-1 may be summarized as follows, treatment of: Type I diabetes, Type II diabetes,

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obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system diseases, restenosis and neurodegenerative diseases. GLP-1 analogues of the present invention that elicit an antagonist effect from a subject can be used for treating the following: hypoglycemia and malabsorption syndrome
5 associated with gastroectomy or small bowel resection.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of formula (I) in association with a pharmaceutically acceptable carrier.

The dosage of active ingredient in the compositions of this invention may be varied;
10 however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. In general, an effective dosage for the activities of this invention is in the range of 1×10^{-7} to 200 mg/kg/day, preferably 1×10^{-4} to 100 mg/kg/day, which can be administered as a single dose or divided
15 into multiple doses.

The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual or topical routes of administration and can be formulated with pharmaceutically acceptable carriers to provide dosage forms appropriate for each route of
20 administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than
25 such inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly
30 used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous

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solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as coca butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

Further, a compound of this invention can be administered in a sustained release composition such as those described in the following patents and patent applications. U.S. Patent No. 5,672,659 teaches sustained release compositions comprising a bioactive agent and a polyester. U.S. Patent No. 5,595,760 teaches sustained release compositions comprising a bioactive agent in a gelable form. U.S. Application No. 08/929,363 filed September 9, 1997, teaches polymeric sustained release compositions comprising a bioactive agent and chitosan. U.S. Application No. 08/740,778 filed November 1, 1996, teaches sustained release compositions comprising a bioactive agent and cyclodextrin. U.S. Application No. 09/015,394 filed January 29, 1998, teaches absorbable sustained release compositions of a bioactive agent. U.S. Application No. 09/121,653 filed July 23, 1998, teaches a process for making microparticles comprising a therapeutic agent such as a peptide in an oil-in-water process. U.S. Application No. 09/131,472 filed August 10, 1998, teaches complexes comprising a therapeutic agent such as a peptide and a phosphorylated polymer. U.S. Application No. 09/184,413 filed November 2, 1998, teaches complexes comprising a therapeutic agent such as a peptide and a polymer bearing a non-polymerizable lactone. The teachings of the foregoing patents and applications are incorporated herein by reference.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Also, all publications, patent applications, patents and other references mentioned herein are incorporated by reference.

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The following examples describe synthetic methods for making a peptide of this invention, which methods are well-known to those skilled in the art. Other methods are also known to those skilled in the art. The examples are provided for the purpose of illustration and is not meant to limit the scope of the present invention in any manner.

5

Example 1

[Aib^{8,35}]hGLP-1(7-36)NH₂

The title peptide was synthesized on an Applied Biosystems (Foster City, CA) model 430A peptide synthesizer which was modified to do accelerated Boc-chemistry solid phase peptide synthesis. See Schnoize, et al., Int. J. Peptide Protein Res., 90:180 (1992). 4-Methylbenzhydrylamine (MBHA) resin (Peninsula, Belmont, CA) with the substitution of 0.93 mmol/g was used. The Boc amino acids (Bachem, CA, Torrance, CA; Nova Biochem., LaJolla, CA) were used with the following side chain protection: Boc-Ala-OH, Boc-Arg(Tos)-OH, Boc-Asp(OcHex)-OH, Boc-Tyr(2BrZ)-OH, Boc-His(DNP)-OH, Boc-Val-OH, Boc-Leu-OH, Boc-Gly-OH, Boc-Gln-OH, Boc-Ile-OH, Boc-Lys(2ClZ)-OH, Boc-Thr(Bzl)-OH, Boc-Ser(Bzl)-OH, Boc-Phe-OH, Boc-Aib-OH, Boc-Glu(OcHex)-OH and Boc-Trp(Fm)-OH. The synthesis was carried out on a 0.20 mmol scale. The Boc groups were removed by treatment with 100% TFA for 2 x 1 min. Boc amino acids (2.5 mmol) were pre-activated with HBTU (2.0 mmol) and DIEA (1.0 mL) in 4 mL of DMF and were coupled without prior neutralization of the peptide-resin TFA salt. Coupling times were 5 min. except for the Boc-Aib-OH residues and the following residues, Boc-Lys(2ClZ)-OH and Boc-His(DNP)-OH wherein the coupling times were 2 hours.

At the end of the assembly of the peptide chain, the resin was treated with a solution of 20% mercaptoethanol/10% DIEA in DMF for 2 x 30 min. to remove the DNP group on the His side chain. The N-terminal Boc group was then removed by treatment with 100% TFA for 2 x 2 min. After neutralization of the peptide-resin with 10% DIEA in DMF (1 x 1 min), the formyl group on the side of the chain of Trp was removed by treatment with a solution of 15% ethanolamine/ 15% water/ 70% DMF for 2 x 30 min. The partially-deprotected peptide-resin was washed with DMF and DCM and dried under reduced pressure. The final cleavage was done by stirring the peptide-resin in 10 mL of HF containing 1 mL of anisole and dithiothreitol (24 mg) at 0°C for 75 min. HF was removed by a flow of nitrogen. The residue was washed with ether (6 x 10 mL) and extracted with 4N HOAc (6 x 10 mL).

The peptide mixture in the aqueous extract was purified on reverse-phase preparative high pressure liquid chromatography (HPLC) using a reverse phase VYDAC® C₁₈ column (Nest Group, Southborough, MA). The column was eluted with a linear gradient

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(20% to 50% of solution B over 105 min.) at a flow rate of 10 mL/min (Solution A = water containing 0.1% TFA; Solution B = acetonitrile containing 0.1% of TFA). Fractions were collected and checked on analytical HPLC. Those containing pure product were combined and lyophilized to dryness. 135 mg of a white solid was obtained. Purity was 98.6% based on analytical HPLC analysis. Electro-spray mass spectrometer analysis gave the molecular weight at 3339.7 (in agreement with the calculated molecular weight of 3339.7).

Example 2



The title compound (HEPES is (4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid)) can be synthesized as follows: after synthesis of the peptide $[\text{His}^7, \text{Aib}^{8,35}]\text{hGLP-1(7-36)NH}_2$ on MBHA resin (0.20 mmol) according to the procedure of Example 1, the peptide-resin is treated with 100% TFA (2 x 2 min.) and washed with DMF and DCM. The resin is then neutralized with 10% DIEA in DMF for 2 min. After washing with DMF and DCM, the resin is treated with 0.23 mmol of 2-chloro-1-ethanesulfonyl chloride and 0.7 mmol of DIEA in DMF for about 1 hour. The resin is washed with DMF and DCM and treated with 1.2 mmol of 2-hydroxyethylpiperazine for about 2 hours. The resin is washed with DMF and DCM and treated with different reagents ((1) 20% mercaptoethanol / 10% DIEA in DMF and (2) 15% ethanolamine / 15% water / 70% DMF) to remove the DNP group on the His side chain and formyl group on the Trp side chain as described above before the final HF cleavage of the peptide from the resin.

Example 3



The title compound (HEPA is (4-(2-hydroxyethyl)-1-piperazineacetyl)) can be made substantially according to the procedure described in Example 2 for making $[(N^{\alpha}\text{-HEPES-His})^7, \text{Aib}^{8,35}]\text{hGLP-1(7-36)NH}_2$ except that 2-bromoacetic anhydride is used in place of 2-chloro-1-ethanesulfonyl chloride.

Example 4



The title compound was synthesized substantially according to the procedure described for Example 1 using the appropriate protected amino acids. MS (ES) = 3325.7, calculated MW = 3325.8, purity = 99%, yield = 85 mg.

The synthesis of other compounds of the present invention can be accomplished in substantially the same manner as the procedure described for the synthesis of $[\text{Aib}^{8,35}]\text{hGLP-1(7-36)NH}_2$ in Example 1 above, but using the appropriate protected amino

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acids depending on the desired peptide.

Example 5



The Boc amino acids used were the same as those in the synthesis of
 5 $[\text{Aib}^{8,35}]\text{hGLP-1(7-36)NH}_2$ described in Example 1 except that Fmoc-Lys(Boc)-OH was used
 in this example. The first amino acid residue was coupled to the resin manually on a
 shaker. 2.5 mmol of Fmoc-Lys(Boc)-OH was dissolved in 4 mL of 0.5N HBTU in DMF. To
 the solution was added 1 mL of DIEA. The mixture was shaken for about 2 min. To the
 solution was then added 0.2 mmol of MBHA resin (substitution = 0.93 mmol/g). The mixture
 10 was shaken for about 1 hr. The resin was washed with DMF and treated with 100% TFA for
 2x2 min to remove the Boc protecting group. The resin was washed with DMF. Myristic acid
 (2.5 mmol) was pre-activated with HBTU (2.0 mmol) and DIEA (1.0 mL) in 4 mL of DMF for
 2 min and was coupled to the Fmoc-Lys-resin. The coupling time was about 1 hr. The resin
 15 was washed with DMF and treated with 25% piperidine in DMF for 2x20 min to remove the
 Fmoc protecting group. The resin was washed with DMF and transferred to the reaction
 vessel of the peptide synthesizer. The synthesis and purification procedures of the
 remainder of the peptide were the same as those in the synthesis of $[\text{Aib}^{8,35}]\text{hGLP-1(7-36)NH}_2$
 in Example 1. 43.1 mg of the title compound was obtained as a white solid. Purity
 was 98% based on analytical HPLC analysis. Electro-spray mass spectrometer analysis
 20 gave the molecular weight at 3577.7 in agreement with the calculated molecular weight
 3578.7.

Examples 6-8

Examples 6-8 were synthesized substantially according to the procedure described
 for Example 5 using the appropriate protected amino acid and the appropriate acid in place
 25 of the Myristic acid used in Example 5.

Example 6: $[\text{Aib}^{8,35}, \text{Arg}^{26}, \text{Lys}^{34}(\text{N}^{\epsilon}\text{-tetradecanoyl})]\text{hGLP-1(7-36)NH}_2$; Yield = 89.6 mg;
 MS(ES) = 3577.2, Calculated MW = 3578.7; Purity 96%.

Example 7: $[\text{Aib}^{8,35,37}, \text{Arg}^{26,34}, \text{Lys}^{38}(\text{N}^{\epsilon}\text{-tetradecanoyl})]\text{hGLP-1(7-38)NH}_2$; Yield = 63.3 mg;
 MS(ES) = 3818.7; Calculated MW = 3819.5; Purity 96%.

30 Example 8: $[\text{Aib}^{8,35}, \text{Arg}^{26,34}, \text{Lys}^{36}(\text{N}^{\epsilon}\text{-decanoyl})]\text{hGLP-1(7-36)NH}_2$; Yield = 57.4 mg;
 MS(ES) = 3521.5; Calculated MW = 3522.7; Purity 98%; Acid = decanoic acid.

The syntheses of other compounds of the present invention containing Lys(N^ε-
 alkanoyl) residue can be carried out in an analogous manner to the procedure described for
 Example 8, $[\text{Aib}^{8,35}, \text{Arg}^{26,34}, \text{Lys}^{36}(\text{N}^{\epsilon}\text{-tetradecanoyl})]\text{hGLP-1(7-36)NH}_2$. Fmoc-Lys(Boc)-OH

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amino acid is used for the residue of Lys(N^ε-alkanoyl) in the peptide, while Boc-Lys(2CIZ)-OH amino acid is used for the residue of Lys. If the Lys(N^ε-alkanoyl) residue is not at the C-terminus, the peptide fragment immediately prior to the Lys(N^ε-alkanoyl) residue is assembled on the resin on the peptide synthesizer first. The appropriate acid corresponding to the desired alkanoyl can be purchased from Aldrich Chemical Co., Inc. Milwaukee, WI, USA, e.g., octanoic acid, decanoic acid, lauric acid and palmitic acid.

Example 9



The Boc amino acids to be used in this synthesis are the same as those used in the synthesis of Example 5. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Lys(Boc)-OH is dissolved in 4 mL of 0.5N HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA resin(substitution = 0.93 mmol/g). The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x2 min to remove the Boc protecting group. The resin is washed with DMF and to it is added 0.25 mmol of 1-dodecanesulfonyl chloride in 4 mL of DMF and 1 mL of DIEA. The mixture is shaken for about 2 hrs. The resin is washed with DMF and treated with 25% piperidine in DMF for 2 x 20 min to remove the Fmoc protecting group. The resin is washed with DMF and transferred to the reaction vessel of the peptide synthesizer. The synthesis of the rest of the peptide and purification procedures are the same as those described in Example 1.

The syntheses of other compounds of the present invention containing Lys(N^ε-alkylsulfonyl) residue can be carried out in an analogous manner to the procedure described in Example 9. Fmoc-Lys(Boc)-OH amino acid is used for the residue of Lys(N^ε-alkylsulfonyl) in the peptide, while Boc-Lys(2CIZ)-OH amino acid is used for the residue of Lys. If the Lys(N^ε-alkylsulfonyl) residue is not at the C-terminus, the peptide fragment immediately prior to the Lys(N^ε-alkylsulfonyl) residue is assembled on the resin on the peptide synthesizer first. The appropriate alkylsulfonyl chloride can be obtained from Lancaster Synthesis Inc., Windham, NH, USA, e.g., 1-octanesulfonyl chloride, 1-decanesulfonyl chloride, 1-dodecanesulfonyl chloride, 1-hexadecanesulfonyl chloride and 1-octadecylsulfonyl chloride.

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Example 10

[Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl)))]hGLP-1(7-36)NH₂

The Boc amino acids to be used for this example are the same as those used in the synthesis of Example 5. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Lys(Boc)-OH is dissolved in 4 mL of 0.5N HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA (substitution = 0.93 mmol/g) resin. The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x2 min to remove the Boc protecting group. The resin is washed with DMF. The 2-bromoacetic acid (2.5 mmol) is pre-activated with HBTU (2.0 mmol) and DIEA (1 mL) in 4 mL of DMF for about 2 min and is added to the resin. The mixture is shaken for about 10 min and washed with DMF. The resin is then treated with 1.2 mmol of piperazine in 4 mL of DMF for about 2 hrs. The resin is washed with DMF and treated with 2 mmol of 1-iodotetradecane for about 4 hrs. After washing with DMF, the resin is treated with 3 mmol of acetic anhydride and 1 mL of DIEA in 4 mL of DMF for about 0.5 hr. The resin is washed with DMF and treated with 25% piperidine in DMF for 2x20 min. The resin is washed with DMF and transferred to the reaction vessel of the peptide synthesizer to continue the synthesis. The synthesis and purification procedures of the remainder of the peptide are the same as the procedures described for Example 1.

The syntheses of other compounds of the present invention containing Lys(N^ε-(2-(4-alkyl-1-piperazine)-acetyl)) residue are carried out in an analogous manner as the procedure described for the synthesis of Example 10. Fmoc-Lys(Boc)-OH amino acid is used for the residue of Lys(N^ε-(2-(4-alkyl-1-piperazine)-acetyl)) in the peptide, while Boc-Lys(2CIZ)-OH amino acid is used for the residue of Lys. The corresponding iodoalkane is used for the residue of Lys(N^ε-(2-(4-alkyl-1-piperazine)-acetyl)) during the alkylation step. If the Lys(N^ε-(2-(4-alkyl-1-piperazine)-acetyl)) residue is not at the C-terminus, the peptide fragment immediately prior to the Lys(N^ε-(2-(4-alkyl-1-piperazine)-acetyl)) residue is assembled on the resin on the peptide synthesizer first.

Example 11

[Aib^{8,35}, Arg^{26,34}, Asp³⁶(1-(4-tetradecyl-piperazine)))]hGLP-1(7-36)NH₂

The Boc amino acids to be used in this example are the same as the amino acids used in synthesis of Example 5 except Fmoc-Asp(O-tBu)-OH is used at position 36 and Boc-Asp(OcHex)-OH is used at position 15. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Asp(O-tBu)-OH is dissolved in 4 mL of 0.5N

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5 HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA (substitution = 0.93 mmol/g) resin. The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x15 min to remove the tBu protecting group. The resin is washed with DMF and is
10 treated with HBTU (0.6 mmol) and DIEA (1mL) in 4 mL of DMF for about 15 min 0.6 mmol of piperazine is added to the reaction mixture and the mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 3 mmol of 1-iodotetradecane for about 4 hrs. After washing with DMF, the resin is treated with 3 mmol of acetic anhydride and 1 mL of DIEA in 4 mL of DMF for about 0.5 hr. The resin is washed with DMF and treated with 25%
15 piperidine in DMF for 2x20 min to remove the Fmoc protecting group. The resin is washed with DMF and transferred to the reaction vessel of the peptide synthesizer to continue the synthesis. The synthesis and purification procedures for the remainder of the peptide are the same as those for the synthesis of Example 1.

20 The syntheses of other compounds of the present invention comprising Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) residue are carried out in an analogous manner as the procedure described for the synthesis of Example 11. Fmoc-Asp(O-tBu)-OH or Fmoc-Glu(O-tBu)-OH amino acid is used for the residue of Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) in the peptide, while Boc-Asp(OcHex)-OH or Boc-Glu(OcHex)-OH amino acid is used for the residue of Asp or Glu. The corresponding iodoalkane is used
25 for the residue of Lys(N^ε-(2-(4-alkyl-1-piperazine)-acetyl)) during the alkylation step. If the Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) residue is not at the C-terminus, the peptide fragment immediately prior to the Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) residue is assembled on the resin on the peptide synthesizer first.

Example 12

25 [Aib^{8,35}, Arg^{26,34}, Asp³⁶(1-tetradecylamino)]hGLP-1(7-36)NH₂

30 The Boc amino acids to be used for this example are the same as those used in Example 5. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Asp(O-tBu)-OH is dissolved in 4 mL of 0.5N HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA (substitution = 0.93 mmol/g) resin. The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x15 min to remove the t-Bu protecting group. The resin is washed with DMF and is treated with HBTU (0.6 mmol) and DIEA (1mL) in 4 mL of DMF for about 15 min 0.6 mmol of 1-tetradecaneamine is added to the reaction mixture and the mixture is shaken for about 1 hr.

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5 The resin is washed with DMF and treated with 25% piperidine in DMF for 2x20 min to remove the Fmoc protecting group. The resin is washed with DMF and transferred to the reaction vessel of the peptide synthesizer to continue the synthesis. The synthesis and purification procedures for the remainder of the peptide of this example are the same as those described for the synthesis of Example 1.

10 The syntheses of other compounds of the present invention containing Asp(1-alkylamino) or Glu(1-alkylamino) residue are carried out in an analogous manner as described for the synthesis of Example 12. Fmoc-Asp(O-tBu)-OH or Fmoc-Glu(O-tBu)-OH amino acid is used for the residue of Asp(1-alkylamino) or Glu(1-alkylamino), respectively, in the peptide, while Boc-Asp(OcHex)-OH or Boc-Glu(OcHex)-OH amino acid is used for the residue of Asp or Glu, respectively. If the Asp(1-alkylamino) or Glu(1-alkylamino) residue is not at the C-terminus, the peptide fragment immediately prior to the Asp(1-alkylamino) or Glu(1-alkylamino) residue is assembled on the resin on the peptide synthesizer first.

15 Example 13

[Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl),β-Ala³⁷]hGLP-1(7-37)-OH

20 The Boc amino acids used are the same as those in the synthesis of [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂ (Example 5). 270 mg of Boc-β-Ala-PAM resin (Novabiochem, San Diego, California, substitution=0.74 mmol/g) was used. The Boc protecting group on Boc-β-Ala-PAM resin was deblocked on a shaker with 100%TFA for 2x2 min first. The remainder of the synthesis and purification procedures were the same as that in Example 5. 83.0 mg of the title peptide was obtained as white solid. Purity was 99% based on analytical HPLC analysis. Electro-spray mass spectrometer analysis gave the molecular weight at 3650.5 in agreement with the calculated weight 3650.8.

25 Example 14

[Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)-OH

30 The Boc amino acids to be used are the same as those in the synthesis of [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂ (Example 5). Fmoc-Lys(Boc)-OH (2.5 mmol) is pre-activated with HBTU (2.0 mmol), HOBt (2.0 mmol and DIEA (2.5 ml) in DMF (4 ml) for about 2 min. This amino acid is coupled to 235 mg of PAM resin (Chem-Impex, Wood Dale, IL; substitution = 0.85 mmol/g) manually on a shaker. The coupling time is about 8 hrs. The remainder of the synthesis and purification procedures are the same as those in Example 5.

The syntheses of other analogs of hGLP-1(7-36)-OH, hGLP-1(7-37)-OH and hGLP-1(7-38)-OH of the instant application, which contain Lys(N^ε-alkanoyl) residue, can be carried out in an analogous manner according to the procedure described for the synthesis of Example 14. Fmoc-Lys(Boc)-OH amino acid is used for the residue of Lys(N^ε-alkanoyl) in the peptide, while Boc-Lys(2CIZ)-OH amino acid is used for the residue of Lys.

The following examples can be made according to the appropriate procedures described hereinabove.

Example 15: [Aib³⁵]hGLP-1(7-36)NH₂

Example 16: [β-Ala³⁵]hGLP-1(7-36)NH₂

10 Example 17: [(N^α-Me-His)⁷, Aib^{8,35}]hGLP-1(7-36)NH₂

Example 18: [(N^α-Me-His)⁷, Aib⁸, β-Ala³⁵]hGLP-1(7-36)NH₂

Example 19: [(N^α-Me-His)⁷, Aib^{8,35}, Arg^{26,34}]hGLP-1(7-36)NH₂

Example 20: [(N^α-Me-His)⁷, Aib⁸, Arg^{26,34}, β-Ala³⁵]hGLP-1(7-36)NH₂

Example 21: [Aib⁸, A6c³⁵]hGLP-1(7-36)NH₂

15 Example 22: [Aib⁸, A5c³⁵]hGLP-1(7-36)NH₂

Example 23: [Aib⁸, D-Ala³⁵]hGLP-1(7-36)NH₂

Example 24: [Aib^{8,35}, A6c³²]hGLP-1(7-36)NH₂

Example 25: [Aib^{8,35}, A5c³²]hGLP-1(7-36)NH₂

Example 26: [Aib^{8,35}, Glu²³]hGLP-1(7-36)NH₂

20 Example 27: [Aib^{8,24,35}]hGLP-1(7-36)NH₂

Example 28: [Aib^{8,30,35}]hGLP-1(7-36)NH₂

Example 29: [Aib^{8,25,35}]hGLP-1(7-36)NH₂

Example 30: [Aib^{8,35}, A6c^{16,20}]hGLP-1(7-36)NH₂

Example 31: [Aib^{8,35}, A6c^{16,29,32}]hGLP-1(7-36)NH₂

25 Example 32: [Aib^{8,35}, A6c^{20,32}]hGLP-1(7-36)NH₂

Example 33: [Aib^{8,35}, A6c²⁰]hGLP-1(7-36)NH₂

Example 34: [Aib^{8,35}, Lys²⁵]hGLP-1(7-36)NH₂

Example 35: [Aib^{8,24,35}, A6c²⁰]hGLP-1(7-36)NH₂

Example 36: [Aib^{8,35}, A6c^{29,32}]hGLP-1(7-36)NH₂

30 Example 37: [Aib^{8,24,35}, A6c^{29,32}]hGLP-1(7-36)NH₂

Example 38: [Aib^{8,35}, A6c¹²]hGLP-1(7-36)NH₂

Example 39: [Aib^{8,35}, Cha²⁰]hGLP-1(7-36)NH₂

Example 40: [Aib^{8,35}, A6c³³]hGLP-1(7-36)NH₂

Example 41: [Aib^{8,35}, A6c^{20,32}]hGLP-1(7-36)NH₂

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- Example 42: [Aib⁸, A6c^{16,20}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 43: [Aib^{8,35}, β-Ala²²]hGLP-1(7-36)NH₂
- Example 44: [Aib^{8,22,35}]hGLP-1(7-36)NH₂
- Example 45: [Aib^{8,35}, Glu²³, A6c³²]hGLP-1(7-36)NH₂
- 5 Example 46: [Aib^{8,24,35}, Glu²³, A6c³²]hGLP-1(7-36)NH₂
- Example 47: [Aib^{8,24,25,35}, Glu²³, A6c³²]hGLP-1(7-36)NH₂
- Example 48: [Aib^{8,24,25,35}, A6c^{16,20,32}, Glu²³]hGLP-1(7-36)NH₂
- Example 49: [Aib⁸, A6c³², β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 50: [Aib⁸, A5c³², β-Ala³⁵]hGLP-1(7-36)NH₂
- 10 Example 51: [Aib⁸, Glu²³, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 52: [Aib^{8,24}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 53: [Aib^{8,30}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 54: [Aib^{8,25}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 55: [Aib⁸, A6c^{16,20}, β-Ala³⁵]hGLP-1(7-36)NH₂
- 15 Example 56: [Aib⁸, A6c^{16,29,32}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 57: [Aib⁸, A6c^{20,32}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 58: [Aib⁸, A6c²⁰, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 59: [Aib⁸, Lys²⁵, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 60: [Aib^{8,24}, A6c²⁰, β-Ala³⁵]hGLP-1(7-36)NH₂
- 20 Example 61: [Aib⁸, A6c^{29,32}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 62: [Aib^{8,24}, A6c^{29,32}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 63: [Aib⁸, A6c¹², β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 64: [Aib⁸, Cha²⁰, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 65: [Aib⁸, A6c³³, β-Ala³⁵]hGLP-1(7-36)NH₂
- 25 Example 66: [Aib⁸, A6c^{20,32}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 67: [Aib⁸, β-Ala^{22,35}]hGLP-1(7-36)NH₂
- Example 68: [Aib^{8,22}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 69: [Aib⁸, Glu²³, A6c³², β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 70: [Aib^{8,24}, Glu²³, A6c³², β-Ala³⁵]hGLP-1(7-36)NH₂
- 30 Example 71: [Aib^{8,24}, Glu²³, A6c³², Lys³⁴(N^ε-octanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 72: [Aib^{8,24,25}, Glu²³, A6c³², β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 73: [Aib^{8,24,25}, A6c^{16,20,32}, Glu²³, β-Ala³⁵]hGLP-1(7-36)NH₂

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- Example 74: [Aib^{8,35}, D-Arg³⁶]hGLP-1(7-36)NH₂
 Example 75: [Aib^{8,35}, D-Lys³⁶]hGLP-1(7-36)NH₂
 Example 76: [Aib⁸, β-Ala³⁵, D-Arg³⁶]hGLP-1(7-36)NH₂
 Example 77: [Aib⁸, β-Ala³⁵, D-Lys³⁶]hGLP-1(7-36)NH₂
 5 Example 78: [Aib^{8,35}, Arg^{26,34}]hGLP-1(7-36)NH₂
 Example 79: [Aib⁸, Arg^{26,34}, β-Ala³⁵]hGLP-1(7-36)NH₂
 Example 80: [Aib^{8,35}, Arg^{25,26,34}]hGLP-1(7-36)NH₂
 Example 81: [Aib⁸, Arg^{25,26,34}, β-Ala³⁵]hGLP-1(7-36)NH₂
 Example 82: [Aib⁸, Arg^{26,34}, β-Ala³⁵, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)OH
 10 Example 83: [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-37)OH
 Example 84: [Aib^{8,35,37}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-37)OH
 Example 85: [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl), D-Ala³⁷]hGLP-1(7-37)OH
 Example 86: [Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)OH
 Example 87: [Aib^{8,35}, Arg^{26,34}, β-Ala³⁷, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)OH
 15 Example 88: [Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)OH
 Example 89: [Aib⁸, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl), β-Ala³⁷]hGLP-1(7-37)OH
 Example 90: [Aib^{8,37}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-37)OH
 Example 91: [Aib^{8,35}, Arg^{26,34}, Ado³⁷]hGLP-1(7-37)OH
 Example 92: [Aib^{8,35}, Arg^{26,34}, Ado³⁷]hGLP-1(7-37)NH₂
 20 Example 93: [Aib⁸, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl), D-Ala³⁷]hGLP-1(7-37)OH
 Example 94: [Aib^{8,37}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)OH
 Example 95: [Aib⁸, Arg^{26,34}, β-Ala³⁷, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)OH
 Example 96: [Aib^{8,35}, Lys²⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
 Example 97: [Aib^{8,35}, Lys²⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
 25 Example 98: [Aib^{8,35}, Lys²⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
 Example 99: [Aib⁸, Lys²⁶(N^ε-octanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
 Example 100: [Aib⁸, Lys²⁶(N^ε-tetradecanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
 Example 101: [Aib⁸, Lys²⁶(N^ε-hexadecanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
 Example 102: [Aib^{8,35}, Lys²⁶(N^ε-octanoyl), Arg³⁴]hGLP-1(7-36)NH₂
 30 Example 103: [Aib^{8,35}, Lys²⁶(N^ε-tetradecanoyl), Arg³⁴]hGLP-1(7-36)NH₂
 Example 104: [Aib^{8,35}, Lys²⁶(N^ε-hexadecanoyl), Arg³⁴]hGLP-1(7-36)NH₂
 Example 105: [Aib^{8,35}, Lys²⁶(N^ε-decanoyl), Arg³⁴]hGLP-1(7-36)NH₂

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- Example 106: [Aib^{8,35}, Lys²⁵, Lys²⁶(N^ε-octanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 107: [Aib^{8,35}, Lys²⁵, Lys²⁶(N^ε-tetradecanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 108: [Aib^{8,35}, Lys²⁵, Lys²⁶(N^ε-hexadecanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 109: [Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- 5 Example 110: [Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 111: [Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 112: [Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-decanoyl)]hGLP-1(7-36)NH₂
- Example 113: [Aib⁸, Lys²⁶(N^ε-octanoyl), Arg³⁴, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 114: [Aib⁸, Lys²⁶(N^ε-tetradecanoyl), Arg³⁴, β-Ala³⁵]hGLP-1(7-36)NH₂
- 10 Example 115: [Aib⁸, Lys²⁶(N^ε-hexadecanoyl), Arg³⁴, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 116: [Aib⁸, Lys²⁶(N^ε-decanoyl), Arg³⁴, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 117: [Aib^{8,35}, Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 118: [Aib^{8,35}, Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 119: [Aib^{8,35}, Lys³⁴(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- 15 Example 120: [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 121: [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 122: [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-decanoyl)]hGLP-1(7-36)NH₂
- Example 123: [Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 124: [Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- 20 Example 125: [Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 126: [Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-decanoyl)]hGLP-1(7-36)NH₂
- Example 127: [Aib^{8,35}, Lys²⁵, Arg²⁶, Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 128: [Aib^{8,35}, Lys²⁵, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 129: [Aib^{8,35}, Lys²⁵, Arg²⁶, Lys³⁴(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- 25 Example 130: [Aib^{8,35}, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 131: [Aib^{8,35}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 132: [Aib^{8,35}, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 133: [Aib^{8,35}, Arg²⁶, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 134: [Aib^{8,35}, Arg²⁶, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- 30 Example 135: [Aib^{8,35}, Arg²⁶, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 136: [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 137: [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂

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- Example 138: [Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-octanoyl)]hGLP-1(7-38)NH₂
- Example 139: [Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-decanoyl)]hGLP-1(7-38)NH₂
- Example 140: [Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)NH₂
- Example 141: [Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-hexadecanoyl)]hGLP-1(7-38)NH₂
- 5 Example 142: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-octanoyl)]hGLP-1(7-38)NH₂
- Example 143: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-decanoyl)]hGLP-1(7-38)NH₂
- Example 144: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)NH₂
- Example 145: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-hexadecanoyl)]hGLP-1(7-38)NH₂
- Example 146: [Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-octanoyl)]hGLP-1(7-38)NH₂
- 10 Example 147: [Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-decanoyl)]hGLP-1(7-38)NH₂
- Example 148: [Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-hexadecanoyl)]hGLP-1(7-38)NH₂
- Example 149: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-octanoyl)]hGLP-1(7-38)NH₂
- Example 150: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-decanoyl)]hGLP-1(7-38)NH₂
- Example 151: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)NH₂
- 15 Example 152: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-hexadecanoyl)]hGLP-1(7-38)NH₂
- Example 153: [Aib^{8,35}, Lys²⁵, Arg^{26,34}, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 154: [Aib^{8,35}, Lys²⁵, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 155: [Aib^{8,35}, Lys²⁵, Arg^{26,34}, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 156: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- 20 Example 157: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 158: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 159: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-decanoyl)]hGLP-1(7-36)NH₂
- Example 160: [Aib⁸, Lys³⁴(N^ε-octanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 161: [Aib⁸, Lys³⁴(N^ε-tetradecanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- 25 Example 162: [Aib⁸, Lys³⁴(N^ε-hexadecanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 163: [Aib⁸, A6c³², Lys³⁴(N^ε-octanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 164: [Aib⁸, Glu²³, Lys³⁴(N^ε-octanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 165: [Aib⁸, Glu²³, A6c³², Lys³⁴(N^ε-octanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 166: [Aib⁸, Arg²⁶, Lys³⁴(N^ε-octanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- 30 Example 167: [Aib⁸, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 168: [Aib⁸, Arg²⁶, Lys³⁴(N^ε-hexadecanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 169: [Aib⁸, Arg²⁶, Lys³⁴(N^ε-decanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂

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- Example 170: [Aib⁸, Arg^{25,26}, Lys³⁴(N^ε-octanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 171: [Aib⁸, Arg^{25,26}, Lys³⁴(N^ε-tetradecanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 172: [Aib⁸, Arg^{25,26}, Lys³⁴(N^ε-hexadecanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 173: [Aib⁸, Arg^{25,26}, Lys³⁴(N^ε-decanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- 5 Example 174: [Aib⁸, Lys²⁵, Arg²⁶, Lys³⁴(N^ε-octanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 175: [Aib⁸, Lys²⁵, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 176: [Aib⁸, Lys²⁵, Arg²⁶, Lys³⁴(N^ε-hexadecanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 177: [Aib⁸, β-Ala³⁵, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 178: [Aib⁸, β-Ala³⁵, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- 10 Example 179: [Aib⁸, β-Ala³⁵, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 180: [Aib⁸, Arg²⁶, β-Ala³⁵, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 181: [Aib⁸, Arg²⁶, β-Ala³⁵, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 182: [Aib⁸, Arg²⁶, β-Ala³⁵, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 183: [Aib⁸, Arg^{26,34}, β-Ala³⁵, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- 15 Example 184: [Aib⁸, Arg^{26,34}, β-Ala³⁵, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 185: [Aib⁸, Arg^{26,34}, β-Ala³⁵, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 186: [Aib⁸, Arg^{26,34}, β-Ala³⁵, Lys³⁶(N^ε-decanoyl)]hGLP-1(7-36)NH₂
- Example 187: [Aib⁸, Lys²⁵, Arg^{26,34}, β-Ala³⁵, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 188: [Aib⁸, Lys²⁵, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- 20 Example 189: [Aib⁸, Lys²⁵, Arg^{26,34}, β-Ala³⁵, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 190: [Aib⁸, Arg^{25,26,34}, β-Ala³⁵, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 191: [Aib⁸, Arg^{25,26,34}, β-Ala³⁵, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 192: [Aib⁸, Arg^{25,26,34}, β-Ala³⁵, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 193: [Aib⁸, Arg^{25,26,34}, β-Ala³⁵, Lys³⁶(N^ε-decanoyl)]hGLP-1(7-36)NH₂
- 25 Example 194: [Aib^{8,35}, Lys²⁶(N^ε-octanoyl), A6c³², Arg³⁴]hGLP-1(7-36)NH₂
- Example 195: [Aib^{8,35}, Lys²⁶(N^ε-tetradecanoyl), A6c³², Arg³⁴]hGLP-1(7-36)NH₂
- Example 196: [Aib^{8,35}, Lys²⁶(N^ε-hexadecanoyl), A6c³², Arg³⁴]hGLP-1(7-36)NH₂
- Example 197: [Aib^{8,35}, A6c³², Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 198: [Aib^{8,35}, A6c³², Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- 30 Example 199: [Aib^{8,35}, A6c³², Lys³⁴(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 200: [Aib^{8,35}, Arg²⁶, A6c³², Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 201: [Aib^{8,35}, Arg²⁶, A6c³², Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂

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- Example 202: [Aib^{8,35}, A6c³², Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 203: [Aib^{8,35}, A6c³², Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 204: [Aib^{8,35}, A6c³², Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 205: [Aib^{8,35}, Arg²⁶, A6c³², Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- 5 Example 206: [Aib^{8,35}, Arg²⁶, A6c³², Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 207: [Aib^{8,35}, Arg²⁶, A6c³², Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 208: [Aib^{8,35}, Arg^{26,34}, A6c³², Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 209: [Aib^{8,35}, Arg^{26,34}, A6c³², Lys³⁶(N^ε-decanoyl)]hGLP-1(7-36)NH₂
- Example 210: [Aib^{8,35}, Arg^{26,34}, A6c³², Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- 10 Example 211: [Aib^{8,35}, Arg^{26,34}, A6c³², Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 212: [Aib^{8,24,35}, Lys²⁶(N^ε-octanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 213: [Aib^{8,24,35}, Lys²⁶(N^ε-tetradecanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 214: [Aib^{8,24,35}, Lys²⁶(N^ε-hexadecanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 215: [Aib^{8,24,35}, Arg²⁶, Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- 15 Example 216: [Aib^{8,24,35}, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 217: [Aib^{8,24,35}, Arg²⁶, Lys³⁴(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 218: [Aib^{8,24,35}, Arg^{26,34}, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 219: [Aib^{8,24,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 220: [Aib^{8,24,35}, Arg^{26,34}, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- 20 Example 221: [Aib^{8,24,35}, Glu²³, A6c³², Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 222: [Aib^{8,35}, Glu²³, Lys²⁶(N^ε-octanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 223: [Aib^{8,35}, Glu²³, Lys²⁶(N^ε-tetradecanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 224: [Aib^{8,35}, Glu²³, Lys²⁶(N^ε-hexadecanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 225: [Aib^{8,35}, Glu²³, Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- 25 Example 226: [Aib^{8,35}, Glu²³, A6c³², Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 227: [Aib^{8,35}, Glu²³, Arg²⁶, Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 228: [Aib^{8,35}, Glu²³, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 229: [Aib^{8,35}, Glu²³, Arg²⁶, Lys³⁴(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 230: [Aib^{8,35}, Glu²³, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- 30 Example 231: [Aib^{8,35}, Glu²³, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 232: [Aib^{8,35}, Glu²³, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 233: [Aib^{8,35}, Glu²³, Arg^{26,34}, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂

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- Example 234: [Aib^{8,35}, Glu²³, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 235: [Aib^{8,35}, Glu²³, Arg^{26,34}, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 236: [Aib^{8,30,35}, Lys²⁶(N^ε-octanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 237: [Aib^{8,30,35}, Lys²⁶(N^ε-tetradecanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- 5 Example 238: [Aib^{8,30,35}, Lys²⁶(N^ε-hexadecanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 239: [Aib^{8,30,35}, Arg²⁶, Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 240: [Aib^{8,30,35}, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 241: [Aib^{8,30,35}, Arg²⁶, Lys³⁴(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 242: [Aib^{8,30,35}, Arg^{26,34}, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- 10 Example 243: [Aib^{8,30,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 244: [Aib^{8,30,35}, Arg^{26,34}, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 245: [Aib^{8,35}, Glu²³, A6c³², Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 246: [Aib^{8,35}, Glu²³, A6c³², Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 247: [Aib^{8,35}, Glu²³, A6c³², Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- 15 Example 248: [Aib^{8,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 249: [Aib^{8,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 250: [Aib^{8,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 251: [Aib^{8,24,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 252: [Aib^{8,24,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- 20 Example 253: [Aib^{8,24,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 254: [Aib^{8,24,30,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 255: [Aib^{8,24,30,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 256: [Aib^{8,24,30,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 257: [(N^α-HEPES-His)⁷, Aib³⁵]hGLP-1(7-36)NH₂
- 25 Example 258: [(N^α-HEPES-His)⁷, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 259: [(N^α-HEPES-His)⁷, Aib⁸, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 260: [(N^α-HEPA-His)⁷, Aib³⁵]hGLP-1(7-36)NH₂
- Example 261: [(N^α-HEPA-His)⁷, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 262: [(N^α-HEPA-His)⁷, Aib⁸, β-Ala³⁵]hGLP-1(7-36)NH₂
- 30 Example 263: [(N^α-tetradecanoyl-His)⁷, Aib³⁵]hGLP-1(7-36)NH₂
- Example 264: [(N^α-tetradecanoyl-His)⁷, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 265: [(N^α-tetradecanoyl-His)⁷, Aib^{8,35}]hGLP-1(7-36)NH₂

- Example 266: [(N^α-tetradecanoyl-His)⁷, Aib⁸, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 267: [(N^α-tetradecanoyl-His)⁷, Arg^{26,34}, Aib³⁵]hGLP-1(7-36)NH₂
- Example 268: [(N^α-tetradecanoyl-His)⁷, Arg^{26,34}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 269: [(N^α-tetradecanoyl-His)⁷, Aib^{8,35}, Arg^{26,34}]hGLP-1(7-36)NH₂
- 5 Example 270: [(N^α-tetradecanoyl-His)⁷, Aib⁸, Arg^{26,34}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 271: [(N^α-tetradecanoyl-His)⁷, Arg^{25,26,34}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 272: [(N^α-tetradecanoyl-His)⁷, Aib^{8,35}, Arg^{25,26,34}]hGLP-1(7-36)NH₂
- Example 273: [(N^α-tetradecanoyl-His)⁷, Aib⁸, Arg^{25,26,34}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 274: [Aib^{8,35}, Lys²⁶(N^ε-octanesulfonyl), Arg³⁴]hGLP-1(7-36)NH₂
- 10 Example 275: [Aib^{8,35}, Lys²⁶(N^ε-dodecanesulfonyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 276: [Aib^{8,35}, Lys²⁶(N^ε-hexadecanesulfonyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 277: [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-octanesulfonyl)]hGLP-1(7-36)NH₂
- Example 278: [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-dodecanesulfonyl)]hGLP-1(7-36)NH₂
- Example 279: [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-hexadecanesulfonyl)]hGLP-1(7-36)NH₂
- 15 Example 280: [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-octanesulfonyl)]hGLP-1(7-36)NH₂
- Example 281: [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-hexadecanesulfonyl)]hGLP-1(7-36)NH₂
- Example 282: [Aib^{8,35}, Asp²⁶(1-(4-decylpiperazine)), Arg³⁴]hGLP-1(7-36)NH₂
- Example 283: [Aib^{8,35}, Asp²⁶(1-(4-dodecylpiperazine)), Arg³⁴]hGLP-1(7-36)NH₂
- Example 284: [Aib^{8,35}, Asp²⁶(1-(4-tetradecylpiperazine)), Arg³⁴]hGLP-1(7-36)NH₂
- 20 Example 285: [Aib^{8,35}, Asp²⁶(1-(4-hexadecylpiperazine)), Arg³⁴]hGLP-1(7-36)NH₂
- Example 286: [Aib^{8,35}, Arg²⁶, Asp³⁴(1-(4-decylpiperazine))]hGLP-1(7-36)NH₂
- Example 287: [Aib^{8,35}, Arg²⁶, Asp³⁴(1-(4-dodecylpiperazine))]hGLP-1(7-36)NH₂
- Example 288: [Aib^{8,35}, Arg²⁶, Asp³⁴(1-(4-tetradecylpiperazine))]hGLP-1(7-36)NH₂
- Example 289: [Aib^{8,35}, Arg²⁶, Asp³⁴(1-(4-hexadecylpiperazine))]hGLP-1(7-36)NH₂
- 25 Example 290: [Aib^{8,35}, Arg^{26,34}, Asp³⁶(1-(4-decylpiperazine))]hGLP-1(7-36)NH₂
- Example 291: [Aib^{8,35}, Arg^{26,34}, Asp³⁶(1-(4-dodecylpiperazine))]hGLP-1(7-36)NH₂
- Example 292: [Aib^{8,35}, Arg^{26,34}, Asp³⁶(1-(4-hexadecylpiperazine))]hGLP-1(7-36)NH₂
- Example 293: [Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-decylpiperazine))]hGLP-1(7-38)NH₂
- Example 294: [Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-dodecylpiperazine))]hGLP-1(7-38)NH₂
- 30 Example 295: [Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-tetradecylpiperazine))]hGLP-1(7-38)NH₂
- Example 296: [Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-hexadecylpiperazine))]hGLP-1(7-38)NH₂
- Example 297: [Aib^{8,35,37}, Arg^{26,34}, Asp³⁸(1-(4-decylpiperazine))]hGLP-1(7-38)NH₂
- Example 298: [Aib^{8,35,37}, Arg^{26,34}, Asp³⁸(1-(4-dodecylpiperazine))]hGLP-1(7-38)NH₂

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- Example 299: [Aib^{8,35,37}, Arg^{26,34}, Asp³⁸(1-(4-tetradecylpiperazine))]hGLP-1(7-38)NH₂
- Example 300: [Aib^{8,35,37}, Arg^{26,34}, Asp³⁸(1-(4-hexadecylpiperazine))]hGLP-1(7-38)NH₂
- Example 301: [Aib^{8,35}, Arg^{25,34}, Asp²⁶(1-(4-decylpiperazine))]hGLP-1(7-36)NH₂
- Example 302: [Aib^{8,35}, Arg^{25,34}, Asp²⁶(1-(4-dodecylpiperazine))]hGLP-1(7-36)NH₂
- 5 Example 303: [Aib^{8,35}, Arg^{25,34}, Asp²⁶(1-(4-tetradecylpiperazine))]hGLP-1(7-36)NH₂
- Example 304: [Aib^{8,35}, Arg^{25,34}, Asp²⁶(1-(4-hexadecylpiperazine))]hGLP-1(7-36)NH₂
- Example 305: [Aib^{8,35}, Arg^{25,26}, Asp³⁴(1-(4-decylpiperazine))]hGLP-1(7-36)NH₂
- Example 306: [Aib^{8,35}, Arg^{25,26}, Asp³⁴(1-(4-dodecylpiperazine))]hGLP-1(7-36)NH₂
- Example 307: [Aib^{8,35}, Arg^{25,26}, Asp³⁴(1-(4-tetradecylpiperazine))]hGLP-1(7-36)NH₂
- 10 Example 308: [Aib^{8,35}, Arg^{25,26}, Asp³⁴(1-(4-hexadecylpiperazine))]hGLP-1(7-36)NH₂
- Example 309: [Aib^{8,35}, Arg^{25,26,34}, Asp³⁶(1-(4-decylpiperazine))]hGLP-1(7-36)NH₂
- Example 310: [Aib^{8,35}, Arg^{25,26,34}, Asp³⁶(1-(4-dodecylpiperazine))]hGLP-1(7-36)NH₂
- Example 311: [Aib^{8,35}, Arg^{25,26,34}, Asp³⁶(1-(4-tetradecylpiperazine))]hGLP-1(7-36)NH₂
- Example 312: [Aib^{8,35}, Arg^{25,26,34}, Asp³⁶(1-(4-hexadecylpiperazine))]hGLP-1(7-36)NH₂
- 15 Example 313: [Aib^{8,35}, Arg^{25,26,34}, Asp³⁸(1-(4-decylpiperazine))]hGLP-1(7-38)NH₂
- Example 314: [Aib^{8,35}, Arg^{25,26,34}, Asp³⁸(1-(4-dodecylpiperazine))]hGLP-1(7-38)NH₂
- Example 315: [Aib^{8,35}, Arg^{25,26,34}, Asp³⁸(1-(4-tetradecylpiperazine))]hGLP-1(7-38)NH₂
- Example 316: [Aib^{8,35}, Arg^{25,26,34}, Asp³⁸(1-(4-hexadecylpiperazine))]hGLP-1(7-38)NH₂
- Example 317: [Aib^{8,35,37}, Arg^{25,26,34}, Asp³⁸(1-(4-decylpiperazine))]hGLP-1(7-38)NH₂
- 20 Example 318: [Aib^{8,35,37}, Arg^{25,26,34}, Asp³⁸(1-(4-dodecylpiperazine))]hGLP-1(7-38)NH₂
- Example 319: [Aib^{8,35,37}, Arg^{25,26,34}, Asp³⁸(1-(4-tetradecylpiperazine))]hGLP-1(7-38)NH₂
- Example 320: [Aib^{8,35,37}, Arg^{25,26,34}, Asp³⁸(1-(4-hexadecylpiperazine))]hGLP-1(7-38)NH₂
- Example 321: [Aib^{8,35}, Arg^{26,34}, Glu³⁶(1-dodecylamino)]hGLP-1(7-36)NH₂
- Example 322: [Aib^{8,35}, Glu²⁶(1-dodecylamino), Arg³⁴]hGLP-1(7-36)NH₂
- 25 Example 323: [Aib^{8,35}, Arg²⁶, Glu³⁴(1-dodecylamino)]hGLP-1(7-36)NH₂
- Example 324: [Aib^{8,35,37}, Arg^{26,34}, Glu³⁸(1-dodecylamino)]hGLP-1(7-38)NH₂
- Example 325: [Aib^{8,35}, Arg³⁴, Lys²⁶(N^ε-(2-(4-decyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂
- Example 326: [Aib^{8,35}, Arg³⁴, Lys²⁶(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂
- 30 Example 327: [Aib^{8,35}, Arg³⁴, Lys²⁶(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂
- Example 328: [Aib^{8,35}, Arg³⁴, Lys²⁶(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂
- Example 329: [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-(2-(4-decyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

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Example 330: [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

Example 331: [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

5 Example 332: [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

Example 333: [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-(2-(4-decyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

Example 334: [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

10 Example 335: [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

Example 336: [Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-decyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

Example 337: [Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

15 Example 338: [Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

Example 339: [Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

Example 340: [Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-decyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

20 Example 341: [Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

Example 342: [Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

25 Example 343: [Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

Example 344: [Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-(2-(4-decyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

Example 345: [Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

30 Example 346: [Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

Example 347: Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

Example 348: [Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-(2-(4-decyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

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- Example 349: [Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂
- Example 350: [Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂
- 5 Example 351: [Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂
- Example 352: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-(2-(4-decyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂
- Example 353: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂
- 10 Example 354: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂
- Example 355: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂
- 15 Example 356: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-decyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂
- Example 357: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂
- Example 358: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂
- 20 Example 359: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂
- Example 360: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-decyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂
- 25 Example 361: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂
- Example 362: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂
- Example 363: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂
- 30

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CLAIMS

What is claimed is:

1. A compound of formula (I),
5 (R²R³)-A⁷-A⁸-A⁹-A¹⁰-A¹¹-A¹²-A¹³-A¹⁴-A¹⁵-A¹⁶-A¹⁷-A¹⁸-A¹⁹-A²⁰-A²¹-A²²-A²³-A²⁴-A²⁵-
A²⁶-A²⁷-A²⁸-A²⁹-A³⁰-A³¹-A³²-A³³-A³⁴-A³⁵-A³⁶-A³⁷-A³⁸-R¹,
(I)
wherein
A⁷ is L-His, Ura, Paa, Pta, Amp, Tma-His, or deleted, provided that when A⁷ is Ura, Paa or
10 Pta, then R² and R³ are deleted;
A⁸ is Ala, D-Ala, Aib, Acc, N-Me-Ala, N-Me-D-Ala or N-Me-Gly;
A⁹ is Glu, N-Me-Glu, N-Me-Asp or Asp;
A¹⁰ is Gly, Acc or Aib;
A¹¹ is Thr or Ser;
15 A¹² is Phe, Acc, Aic, Aib, 3-Pal, 4-Pal, β-Nal, Cha, Trp or X¹-Phe;
A¹³ is Thr or Ser;
A¹⁴ is Ser or Aib;
A¹⁵ is Asp or Glu;
A¹⁶ is Val, Acc, Aib, Leu, Ile, Tle, Nle, Abu, Ala or Cha;
20 A¹⁷ is Ser or Thr;
A¹⁸ is Ser or Thr;
A¹⁹ is Tyr, Cha, Phe, 3-Pal, 4-Pal, Acc, β-Nal or X¹-Phe;
A²⁰ is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Val, Phe or X¹-Phe;
A²¹ is Glu or Asp;
25 A²² is Gly, Acc, β-Ala or Aib;
A²³ is Gln, Asp, Asn or Glu;
A²⁴ is Ala, Aib, Val, Abu, Tle or Acc;
A²⁵ is Ala, Aib, Val, Abu, Tle, Acc, Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or
HN-CH((CH₂)_e-X³)-C(O);
30 A²⁶ is Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)_e-X³)-C(O);
A²⁷ is Glu or Asp;
A²⁸ is Phe, Pal, β-Nal, X¹-Phe, Aic, Acc, Aib, Cha or Trp;
A²⁹ is Ile, Acc, Aib, Leu, Nle, Cha, Tle, Val, Abu, Ala or Phe;
A³⁰ is Ala, Aib or Acc;

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- A^{31} is Trp, β -Nal, 3-Pal, 4-Pal, Phe, Acc, Aib or Cha;
 A^{32} is Leu, Acc, Aib, Nle, Ile, Cha, Tie, Phe, X^1 -Phe or Ala;
 A^{33} is Val, Acc, Aib, Leu, Ile, Tie, Nle, Cha, Ala, Phe, Abu or X^1 -Phe;
 A^{34} is Lys, Arg, hArg, Orn, $\text{HN-CH}((\text{CH}_2)_n\text{-N(R}^{10}\text{R}^{11}))\text{-C(O)}$ or $\text{HN-CH}((\text{CH}_2)_e\text{-X}^3)\text{-C(O)}$;
5 A^{35} is Gly, β -Ala, D-Ala, Gaba, Ava, $\text{HN-(CH}_2)_m\text{-C(O)}$, Aib, Acc or a D-amino acid;
 A^{36} is L- or D-Arg, D- or L-Lys, D- or L-hArg, D- or L-Orn, $\text{HN-CH}((\text{CH}_2)_n\text{-N(R}^{10}\text{R}^{11}))\text{-C(O)}$, $\text{HN-CH}((\text{CH}_2)_e\text{-X}^3)\text{-C(O)}$ or deleted;
 A^{37} is Gly, β -Ala, D-Ala, Gaba, Ava, $\text{HN-(CH}_2)_m\text{-C(O)}$, Aib, Acc, Ado, a D-amino acid or deleted;
10 A^{38} is D- or L-Lys, D- or L-Arg, D- or L-hArg, D- or L-Orn, $\text{HN-CH}((\text{CH}_2)_n\text{-N(R}^{10}\text{R}^{11}))\text{-C(O)}$, $\text{HN-CH}((\text{CH}_2)_e\text{-X}^3)\text{-C(O)}$ or deleted;

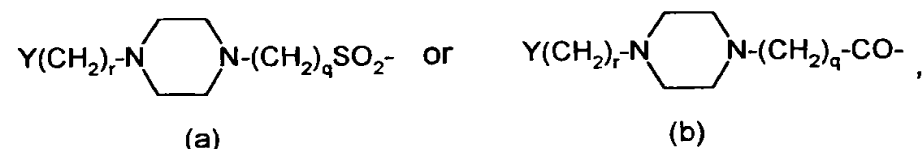
X^1 for each occurrence is independently selected from the group consisting of $(\text{C}_1\text{-C}_6)\text{alkyl}$, OH and halo;

R^1 is OH, NH_2 , $(\text{C}_1\text{-C}_{30})\text{alkoxy}$, or $\text{NH-X}^2\text{-CH}_2\text{-Z}$, wherein X^2 is a $(\text{C}_1\text{-C}_{30})\text{hydrocarbon}$ moiety, and Z is H, OH, CO_2H or CONH_2 ;

X^3 is $\text{X}^4\text{-N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \quad \text{---} \end{array} \text{N-(CH}_2)_f\text{-CH}_3$ or -C(O)-NHR^{12} , wherein X^4 for each occurrence is independently -C(O)- , -NH-C(O)- or $\text{-CH}_2\text{-}$, and f for each occurrence is independently an integer from 1 to 29;

each of R^2 and R^3 is, independently selected from the group consisting of H, $(\text{C}_1\text{-C}_{30})\text{alkyl}$, $(\text{C}_2\text{-C}_{30})\text{alkenyl}$, phenyl $(\text{C}_1\text{-C}_{30})\text{alkyl}$, naphthyl $(\text{C}_1\text{-C}_{30})\text{alkyl}$, hydroxy $(\text{C}_1\text{-C}_{30})\text{alkyl}$, hydroxy $(\text{C}_2\text{-C}_{30})\text{alkenyl}$, hydroxyphenyl $(\text{C}_1\text{-C}_{30})\text{alkyl}$, and

hydroxynaphthyl $(\text{C}_1\text{-C}_{30})\text{alkyl}$; or one of R^2 and R^3 is $(\text{CH}_3)_2\text{-N} \begin{array}{c} \uparrow \\ \text{---} \end{array} \text{C}^+=\text{N}^+(\text{CH}_3)_2$, $(\text{C}_1\text{-C}_{30})\text{acyl}$, $(\text{C}_1\text{-C}_{30})\text{alkylsulfonyl}$, C(O)X^5 ,



where Y is H, OH or NH_2 ; r is 0 to 4; q is 0 to 4; X^5 is $(\text{C}_1\text{-C}_{30})\text{alkyl}$, $(\text{C}_2\text{-C}_{30})\text{alkenyl}$, phenyl $(\text{C}_1\text{-C}_{30})\text{alkyl}$, naphthyl $(\text{C}_1\text{-C}_{30})\text{alkyl}$, hydroxy $(\text{C}_1\text{-C}_{30})\text{alkyl}$,

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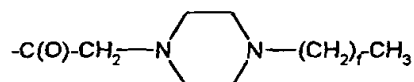
hydroxy(C₂-C₃₀)alkenyl, hydroxyphenyl(C₁-C₃₀)alkyl or hydroxynaphthyl(C₁-C₃₀)alkyl;

e for each occurrence is independently an integer from 1 to 4;

m for each occurrence is independently an integer from 5-24;

5 n for each occurrence is independently an integer from 1-5;

R¹⁰ and R¹¹ for each occurrence is each independently H, (C₁-C₃₀)alkyl, (C₁-C₃₀)acyl, (C₁-C₃₀)alkylsulfonyl, -C((NH)(NH₂)) or



, provided that when R¹⁰ is (C₁-C₃₀)acyl, (C₁-



C₃₀)alkylsulfonyl, -C((NH)(NH₂)) or

, R¹¹ is H or

10 (C₁-C₃₀)alkyl; and

R¹² is (C₁-C₃₀)alkyl;

with the proviso that:

(i) at least one amino acid of a compound of formula (I) is not the same as the native sequence of hGLP-1(7-36, -37 or -38)NH₂ or hGLP-1(7-36, -37 or -38)OH;

15 (ii) a compound of formula (I) is not an analogue of hGLP-1(7-36, -37 or -38)NH₂ or hGLP-1(7-36, -37 or -38)OH wherein a single position has been substituted by Ala;

(iii) a compound of formula (I) is not [Arg^{26,34}, Lys³⁸]hGLP-1(7-38)-E, [Lys²⁶(N^ε-alkanoyl)]hGLP-1(7-36, -37 or -38)-E, [Lys³⁴(N^ε-alkanoyl)]hGLP-1(7-36, -37 or -38)-E, [Lys^{26,34}-bis(N^ε-alkanoyl)]hGLP-1(7-36, -37 or -38)-E, [Arg²⁶, Lys³⁴(N^ε-alkanoyl)]hGLP-1(8-36, -37 or -38)-E, [Arg^{26,34}, Lys³⁶(N^ε-alkanoyl)]hGLP-1(7-36, -37 or -38)-E or [Arg^{26,34}, Lys³⁸(N^ε-alkanoyl)]hGLP-1(7-38)-E, wherein E is -OH or -NH₂;

(iv) a compound of formula (I) is not Z-hGLP-1(7-36, -37 or -38)-OH, Z-hGLP-1(7-36, -37 or -38)-NH₂, where Z is selected from the group consisting of

25 (a) [Arg²⁶], [Arg³⁴], [Arg^{26,34}], [Lys³⁶], [Arg²⁶, Lys³⁶], [Arg³⁴, Lys³⁶], [D-Lys³⁶], [Arg³⁶], [D-Arg³⁶], [Arg^{26,34}, Lys³⁶] or [Arg^{26,36}, Lys³⁴];

(b) [Asp²¹];

(c) at least one of [Aib⁶], [D-Ala⁶] and [Asp⁹]; and

(d) [Tyr⁷], [N-acyl-His⁷], [N-alkyl-His⁷], [N-acyl-D-His⁷] or [N-alkyl-D-His⁷];

30 (v) a compound of formula (I) is not a combination of any two of the substitutions listed in groups (a) to (d); and

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(vi) a compound of formula (I) is not [N-Me-Ala⁸]hGLP-1(8-36 or -37), [Glu¹⁵]hGLP-1(7-36 or -37), [Asp²¹]hGLP-1(7-36 or -37) or [Phe³¹]hGLP-1(7-36 or -37).

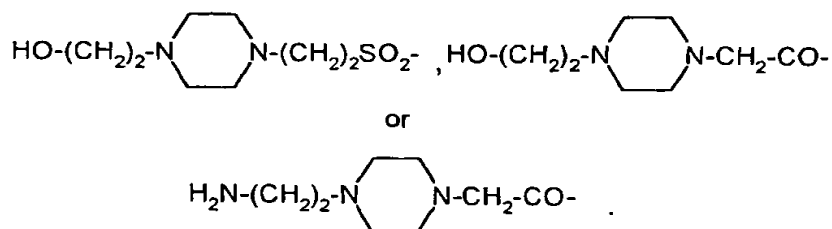
2. A compound according to claim 1, wherein A¹¹ is Thr; A¹³ is Thr; A¹⁵ is Asp; A¹⁷ is Ser; A¹⁸ is Ser; A²¹ is Glu; A²³ is Gln or Glu; A²⁷ is Glu; and A³¹ is Trp; or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 2, wherein A⁹ is Glu, N-Me-Glu or N-Me-Asp; A¹² is Phe, Acc or Aic; A¹⁶ is Val, Acc or Aib; A¹⁹ is Tyr; A²⁰ is Leu, Acc or Cha; A²⁴ is Ala, Aib or Acc; A²⁵ is Ala, Aib, Acc, Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)_e-X³)-C(O); A²⁸ is Phe; A²⁹ is Ile or Acc; A³⁰ is Ala or Aib; A³² is Leu, Acc or Cha; and A³³ is Val or Acc; or a pharmaceutically acceptable salt thereof.

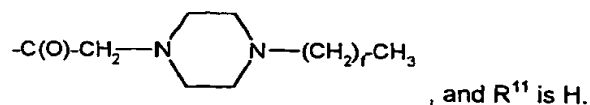
4. A compound according to claim 3, wherein A⁸ is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A¹⁰ is Gly; A¹² is Phe, A6c or A5c; A¹⁶ is Val, A6c or A5c; A²⁰ is Leu, A6c, A5c or Cha; A²² is Gly, β-Ala or Aib; A²⁴ is Ala or Aib; A²⁹ is Ile, A6c or A5c; A³² is Leu, A6c, A5c or Cha; A³³ is Val, A6c or A5c; A³⁵ is Aib, β-Ala, Ado, A6c, A5c or Gly; and A³⁷ is Gly, Aib, β-Ala, Ado, D-Ala or deleted; or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 4 or a pharmaceutically acceptable salt thereof, wherein X⁴ for each occurrence is -C(O)-; e for each occurrence is independently 1 or 2; and R¹ is OH or NH₂.

6. A compound according to claim 5 or a pharmaceutically acceptable salt thereof, wherein R² is H and R³ is (C₁-C₃₀)alkyl, (C₂-C₃₀)alkenyl, (C₁-C₃₀)acyl, (C₁-C₃₀)alkylsulfonyl,

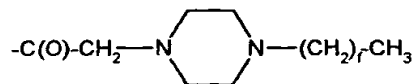


7. A compound according to claim 5 or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is (C₁-C₃₀)acyl, (C₁-C₃₀)alkylsulfonyl or



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8. A compound according to claim 7 or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is (C₄-C₂₀)acyl, (C₄-C₂₀)alkylsulfonyl or



9. A compound according to claim 1 wherein said compound is

- 5 [Aib^{8,35}]hGLP-1(7-36)NH₂,
 [(N^ε-HEPES-His)⁷, Aib^{8,35}]hGLP-1(7-36)NH₂,
 [(N^ε-HEPA-His)⁷, Aib^{8,35}]hGLP-1(7-36)NH₂,
 [Aib⁸, β-Ala³⁵]hGLP-1(7-36)NH₂,
 [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂,
 10 [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂,
 [Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)NH₂,
 [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-decanoyl)]hGLP-1(7-36)NH₂,
 [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-dodecanesulfonyl)]hGLP-1(7-36)NH₂,
 [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂,
 15 [Aib^{8,35}, Arg^{26,34}, Asp³⁶(1-(4-tetradecyl-piperazine))]hGLP-1(7-36)NH₂,
 [Aib^{8,35}, Arg^{26,34}, Asp³⁶(1-tetradecylamino)]hGLP-1(7-36)NH₂,
 [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl), β-Ala³⁷]hGLP-1(7-37)-OH or
 [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)-OH, or a pharmaceutically acceptable salt thereof.
 20 10. A compound according to claim 9 wherein said compound is
 [Aib^{8,35}]hGLP-1(7-36)NH₂,
 [Aib⁸, β-Ala³⁵]hGLP-1(7-36)NH₂,
 [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂,
 [Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)NH₂,
 25 [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-decanoyl)]hGLP-1(7-36)NH₂, or
 [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl), β-Ala³⁷]hGLP-1(7-37)-OH, or a pharmaceutically acceptable salt thereof.
 11. A pharmaceutical composition comprising an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

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12. A method of eliciting an agonist effect from a GLP-1 receptor in a subject in need thereof which comprises administering to said subject an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

5 13. A method of treating a disease selected from the group consisting of Type I diabetes, Type II diabetes, obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system disease, restenosis and neurodegenerative disease, in a subject in need thereof which comprises administering to said subject an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

10 14. A method according to claim 13 wherein said disease is Type I diabetes or Type II diabetes.

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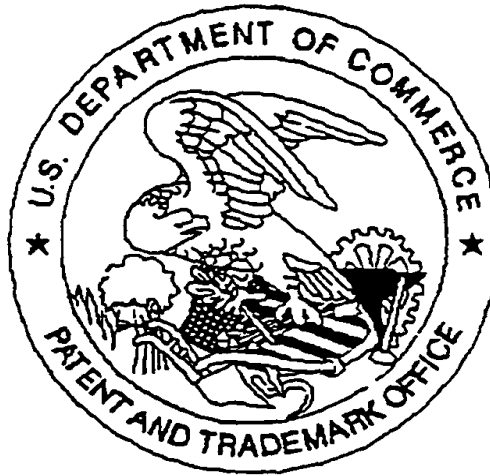
ABSTRACT

The present invention is directed to peptide analogues of glucagon-like peptide-1, the pharmaceutically-acceptable salts thereof, to methods of using such analogues to treat mammals and to pharmaceutical compositions useful therefor comprising said analogues.

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